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BRONCHIOLITIS AND CHRONIC LUNG DISEASE

By K. H. McLean
Department of Pathology, University of Melbourne, Australia

Not infrequently, a fresh view of a subject leads to greater understanding. The pathological evolution of bronchiectasis, emphysema and pulmonary fibrosis cannot be said to be clearly understood, and a new approach to this question has arisen from a morphological study of the natural history of bronchiolar inflammation, the conclusions of which are presented here.

In order to focus attention on the small bronchioles, some aspects of the normal structure and function of the air passages of the lungs require a somewhat different emphasis from that which is ordinarily given.

The Normal Air Passages

a. Structure. These arise by repeated dichotomous division from the trachea. The first divisions, the bronchi, eventually lose the cartilage in their walls and become bronchioles, of which there are approximately six divisions. Beyond the terminal bronchiole, individual thin-walled diverticula, the alveoli, are found with increasing frequency in the respiratory bronchioles, of which there are usually three divisions. This process of " alveolarisation " is complete in more distal divisions, the alveolar ducts and atria, the atria ending in alveolar sacs (Fig. 1).

Thus the respiratory bronchioles are transitional between the purely air-conducting " proximal " passages and those which are also concerned with gas exchange, termed here " distal " air passages. These distal passages communicate with those adjacent by means of defects in the alveolar walls—the alveolar pores (of Cohn) (Macklin, 1936; Loosli, 1937). Air flow through these pores, or collateral ventilation, occurs relatively freely, and ordinarily maintains aeration of the distal passages in the event of proximal obstruction of the air-conducting system (van Allen, Lindskog and Richter, 1931).

b. Function. Several homœostatic mechanisms act to maintain the patency of the airways, which is constantly threatened not only by mucus but also, in special circumstances, by inflammatory exudate and aspirated exogenous fluids.

These mechanisms, which are discussed more fully elsewhere (McLean, 1956b), depend on ciliary action, cough and collateral ventilation. The cilia of the larger bronchioles and the bronchi are constantly moving a sheet of mucus up the trachea into the pharynx (Florey, 1954). Even moderate

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hypersecretion results in the formation of masses of mucus which, in the large bronchi and trachea, elicit the cough reflex. Here, ejection is the obvious result, but in the inspiratory phase mucus may readily be aspirated into the smaller non-ciliated bronchioles; ordinarily it is aspirated only as far as the respiratory bronchioles (Fig. 2), and, moreover, what little may enter the distal passages is readily phagocytosed (McLean, 1956b).

A conclusion of this study was that total obstruction of small bronchioles is an everyday event, but since aeration is ordinarily maintained by collateral ventilation, the plugs are soon expelled by coughing. (These observations are supported by study of normal bronchograms, as long as it is realised that " alveolar filling " is, in fact, filling to the level of the respiratory bronchioles.)

It is important to appreciate that a considerable degree of generalised bronchiolar obstruction can exist without significant reduction in lung function, as long as collateral ventilation is free (Lindskog and Bradshaw, 1934). (Indeed, it is this which makes bronchography possible.) This applies whether the obstruction is due to mucus, inflammatory exudate (as in uncomplicated influenza) or permanent inflammatory obliteration of the bronchioles (*vide infra*).

THE NATURAL HISTORY OF BRONCHIOLAR INFLAMMATION

A. *Establishment*

The establishment of the exudative phase of acute bronchiolitis has been studied (McLean 1956b), with the following conclusions:

Respiratory tract inflammation is a commonplace occurrence in people of all ages. Certain agents are repeatedly involved; these are viruses, chemical agents and pyogenic bacteria.

Viral and chemical inflammation affects the whole respiratory tract, producing extensive ciliary damage, abundant exudate and, often, necrosis and desquamation of the surface epithelium. Bronchiolar obstruction is diffuse but, unless overwhelming, homœostatic mechanisms maintain sufficient bronchioles patent at any one time to allow, by means of collateral ventilation, normal or near normal gas exchange.

Pyogenic bacterial inflammation has points of difference, since such bacteria, even those of considerable virulence, frequently enter the lungs without harmful effects in inspired air and in mucus aspirated from the naso-pharynx. The establishment of inflammation requires the development of a high local concentration of organisms, circumstances ordinarily only provided by prolonged retention of infected plugs occluding bronchioles (Fig. 3); such a degree of stasis is rare in the larger air passages. Thus the establishment of bacterial inflammation depends largely on defective homœostasis.

Moreover, both viral and chemical inflammation are generally of limited duration, but pyogenic bacterial infections persist as long as homœostasis remains defective. It is this possibility of prolonged inflammation which puts special emphasis on the bacterial phase of respiratory tract infections.

Homœostasis in the air passages may be defective because of overload or damage to the mechanisms described. Common examples include:

PLATE XIV

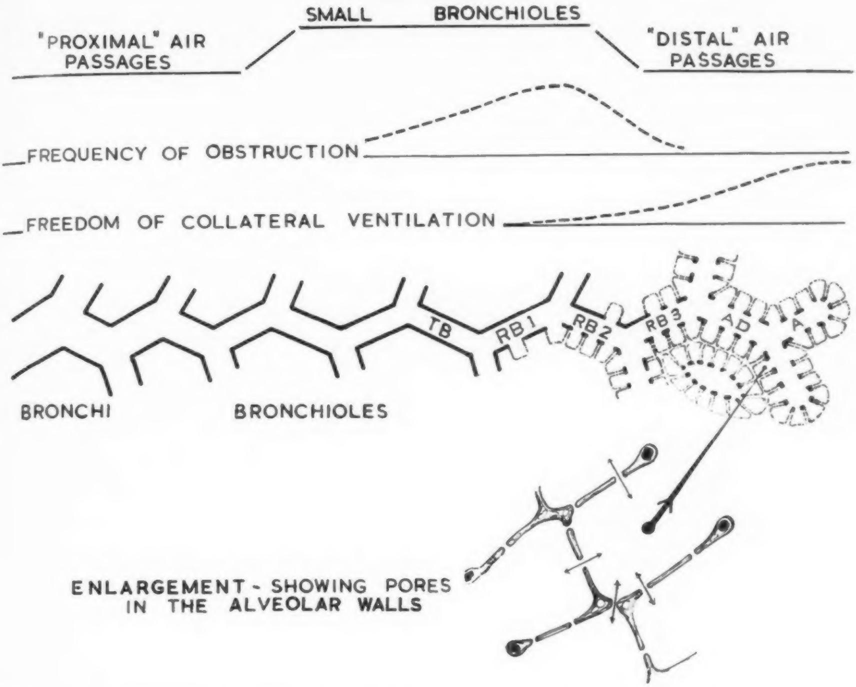
SMALL BRONCHIOLES
"PROXIMAL" AIR PASSAGES
"DISTAL" AIR PASSAGES
FREQUENCY OF OBSTRUCTION
FREEDOM OF COLLATERAL VENTILATION
TB
RB1
RB2
RB3
AD
A
BRONCHI
BRONCHIOLES
ENLARGEMENT - SHOWING PORES IN THE ALVEOLAR WALLS

FIG. 1.—A diagrammatic representation of the normal divisions of the bronchial tree showing bronchi dividing into bronchioles; the terminal bronchiole (TB) divides into three orders of respiratory bronchioles (RB1-3), distal to which are the alveolar ducts (AD) and then atria (A) ending in alveolar sacs. The distribution of alveoli is depicted, part being enlarged to show the alveolar pores.

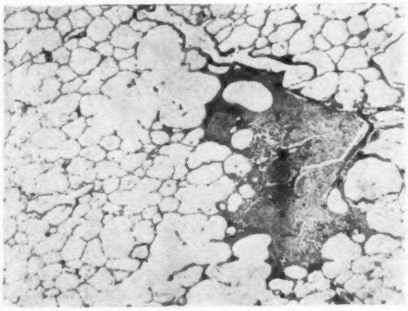

FIG. 2.—Photomicrograph showing the immediate divisions of a first order respiratory bronchiole occluded by mucus (right). The more distal divisions are aerated by collateral ventilation (left). (H. and E. × 13·3).

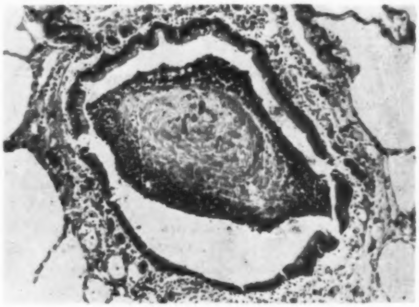

FIG. 3.—Photomicrograph of a small bronchiole in the lung of a patient with a terminal respiratory infection. The plug has shrunk in processing, but the accumulation of polymorphonuclear leucocytes on the periphery indicate that the plug (in which large numbers of bacteria were demonstrated) had been static at this site for sometime before death. (H. and E., × 60.)

PLATE XV

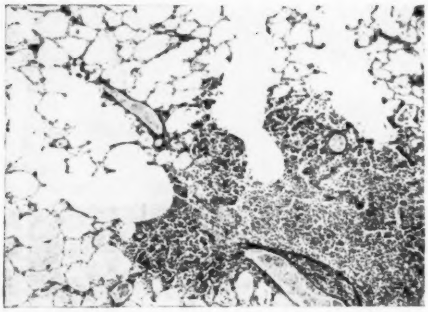

FIG. 4.—Photomicrograph showing acute bronchiolitis in a child; obstruction by exudate and inflammatory cells extends down to the level of the respiratory bronchioles, involving their alveoli. More peripheral passages are uninvolved and remain aerated. (Elastin stain, ×20.)

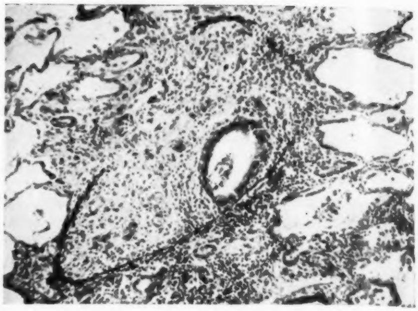

FIG. 5.—Photomicrograph showing an unusually clear example of recent occlusion of a respiratory bronchiole in a child with fibro-cystic disease of the pancreas. The original lumen is indicated by darkly-stained elastic fibres, remnants of the sub-epithelial net of *elastica*. The epithelium lined space is a surviving branch, all other branches having been obliterated. (Elastin stain, ×60.)

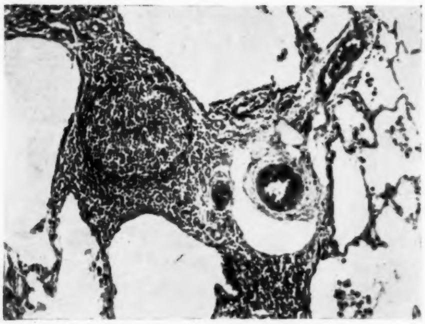

FIG. 6.—The patient had diffuse bronchiectasis of the type described by Whitwell (1952). In serial sections no bronchiole accompanied the pulmonary arterial branch shown in the photomicrograph, and branches of this vessel supplied distal passages with no direct bronchiolar communications. Emphysematous air spaces surround the area. In such lesions relatively few small bronchioles escape obliteration. (H. and E., ×60.)

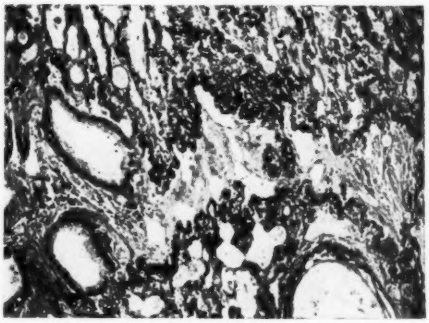

FIG. 7.—Photomicrograph showing an obliterated bronchiole in a small pulmonary scar. A branch of surviving bronchioles at the base of the scar (left) is occluded by vascular connective tissue, the original lumen being outlined by the remnants of the sub-epithelial elastic net, sufficient remaining to permit easy recognition. (Elastin stain ×60.)

1. Overload.
    i. Narrow air passages:
        children, bronchospasm.
    ii. Viscid mucus:
        asthma, fibro-cystic disease of the pancreas.
    iii. Excess fluid:
        exudate, mucus, aspirated fluids.
2. Damage.
    i. Collateral ventilation reduced or abolished:
        occlusion of lobar bronchus,
        occlusion of alveolar pores.
    ii. Cough ineffective:
        general: coma, paralysis.
        local: partial bronchial obstruction.
    iii. Ciliary activity depressed or cilia destroyed:
        viral infections.

It was also concluded that the establishment of the common pyogenic bacterial infections necessitates some degree of failure of the mechanisms maintaining patency of the airways; in other words, an obstructive element always exists as the basis of the establishment of the infection. The initial lesion is essentially acute bronchiolitis, inflammation (and obstruction) extending only to the level of the respiratory bronchioles (Fig. 4). The more virulent organisms, however, establish both more rapidly and more readily and tend to spread beyond the lumen of the bronchiole, so that the obstructive element is rarely as obvious as it is with the less virulent group. Thus it is clinically convenient to divide bacterial lung infections into (obviously) obstructive and (apparently) non-obstructive.

B. The Repair Phase

This was also studied (McLean, 1957a) and it was concluded that some degree of bronchiolar damage frequently follows acute bronchiolitis. Damage to the specialised tissues of the bronchiolar wall was found to be common and was often associated with occlusive processes, of which the most important was complete obliteration. Significant partial obliteration of these small passages was uncommon and presumably readily progresses to the complete form (Fig. 5).

Evidence of diffuse bronchiolar damage and obliteration was regularly found in macroscopically normal lungs of adults who gave no history of severe respiratory infections, so that it was concluded that they were the result of the common minor respiratory infections. In macroscopically damaged lungs, bronchiolar wall damage and obliteration were much more extensive.

It was considered that there are two main reasons why these observations have not been more widely appreciated: First, the technical aspects are forbidding, since the only adequate method of study is the reconstruction of the tissue from serial histological sections; nothing is more misleading than examination of single sections. Secondly, the evolution of these lesions has received little attention from morphologists. Even a relatively limited study of this kind demonstrates the complexity of the problem, particularly in relation to bronchiolar obliteration. Difficulties are created by new formation of specialised tissues, extensive architectural remodelling and the virtual disappearance of the residual strands of connective tissue representing obliterated bronchioles.

However, it was possible to conclude that all respiratory tract inflammations produced some degree of damage, the degree generally depending not so much on the nature of the agent as on the efficiency of the homœostatic mechanisms that have already been discussed.

If a single inflamed bronchiole is considered, the liability to permanent damage, including obliteration, is related to the duration of obstruction by the occluding plug as well as to the severity of the inflammation. This seems eminently reasonable if the bronchioles are thought of as tiny thin-walled tubes which are constantly exposed both to occlusion by mucus and also to an array of damaging agents—a situation unique in the organs of the body.

Bronchiolitis and Chronic Lung Disease

The morphological forms of chronic lung disease can be divided into three main groups: bronchiectasis, pulmonary fibrosis and emphysema. Each has clinical, radiological and pathological features which are frequently sufficiently clear cut to make this separation into three useful. However, the distinction, which is dependent on different morphological features, is not mutually exclusive and all three often occur together.

Each is regarded as resulting from unresolved bronchiolar inflammation, particularly that due to agents already discussed. Many of the factors determining which morphological change is most prominent (that is, which clinical diagnosis will be made) can be recognised readily and the group given an unaccustomed unity.

It has already been explained that acute bronchiolitis is the basic lesion in the commoner forms of respiratory tract inflammation, and that some degree of permanent damage, including bronchiolar obliteration, frequently follows. The factors influencing the severity of permanent bronchiolar damage have been dealt with briefly. What remains therefore is to consider the influence of this damage, and of bronchiolar obliteration in particular, on the remainder of the air passages of the lung, both proximally (larger bronchioles, bronchi and trachea) and distally (some divisions of the respiratory bronchioles, and the alveolar ducts, atria and alveolar sacs).

a. Effects on the Proximal Air Passages

The most important effect of obliteration of the smaller bronchioles on these passages is decreased efficiency of expulsion of excess mucus or exudate.

A moderate degree of bronchiolar obliteration has the effect of prolonging the bacterial phase of respiratory infections, and a greater degree of change may prolong it indefinitely in the absence of treatment (McLean, 1957c).

Extensive bronchiolar obliteration is also associated with structural changes in the larger air passages. Of these dilation (ectasia) is the most obvious, and where this change is gross the diagnosis of bronchiectasis is made. It has long been recognised that the peripheral divisions of an ectatic bronchus are extensively obliterated, but this aspect of the morphology of bronchiectasis has always been overshadowed by the readily demonstrable ectasia. Some dilatation of surviving bronchioles or bronchi can be found in any form of chronic lung disease (McLean, 1956a), but gross changes occur in circumstances which may be predicted from what has already been discussed, since the essential lesion is an extreme degree of bronchiolar obliteration in the affected part.

These circumstances fall into two groups.

(i) *Localised Forms*

Here there is (or was) recognisable reason for extreme bronchiolar obliteration within the affected part of the lung. One common cause is prolonged collapse of a lobe. Occlusion of the lobar bronchus of an anatomically distinct lobe inevitably leads to air absorption and collapse, since there is no path for collateral ventilation (van Allen and Jung, 1931). Prolonged lobar collapse occurs predominantly in infants and children because their soft, small lobar bronchi are easily occluded, and because enlargement of hilar lymph nodes, perhaps the commonest cause of prolonged lobar collapse, is a feature of many infections occurring in this age group.

Another cause is stenosis of a large bronchus (for instance, by a tuberculous stricture or an enlarged gland). This lesion will interfere considerably with the efficacy of those mechanisms expelling material within the lumens of more peripheral passages, and subsequently, extensive bronchiolar obliteration results, particularly following respiratory infections.

(ii) *The Generalised Form*

This has been recognised clinically only recently (Whitwell, 1952). It might be termed "progressive bronchiolitis," since the condition starts in infants and young children and progresses in a series of tenacious respiratory infections. Such lungs show widespread bronchiolar obliteration (Fig. 6) and, typically, bilateral basal bronchiectasis. The whole lung is affected and it is this group of patients which so regularly disappoints thoracic surgeons. Whatever is done for the patient, clinical emphysema in later years would appear to be unavoidable.

The ætiology of the dilatation of the larger air passages that is the feature of bronchiectasis, is vexed. It must be pointed out that only gross forms are labelled bronchiectasis and that some degree of dilatation, seen best in the bronchioles, is regularly found in lungs showing fibrosis or emphysema, both in generalised and in localised lesions (McLean, 1956a). The affected bronchus (or bronchiole) may be surrounded by aerated or even emphysematous lung, so that traction on the wall by surrounding collapsed lung cannot be an important cause of the lesion.

However, common to all ectatic bronchi and bronchioles are both loss of elastic and muscle tissue in their walls and high-grade bronchiolar oliteration distally (McLean, 1957c). While it has been objected that " ectatic " bronchi may contain large amounts of muscle in their walls (Medlar, 1955), such bronchi, which are always found in contracted lobes, also contain excess cartilage and can be shown to be shortened proximal bronchi of approximately normal diameter; the ectatic bronchi are more peripheral.

It is generally agreed that there is retention of secretions in bronchiectasis. Following subsequent prolonged bacterial infection, obliteration extends proximally to the level at which simple mechanical drainage, due to postural changes, empties bronchi sufficiently often to prevent complete organisation. Surviving bronchi are filled with secretion for long periods (McLean, 1956b), particularly during and after respiratory infections, and in these inflammatory episodes the intraluminal pressure will rise, owing to the outpouring of exudate into the poorly drained tube. It is suggested that it is this force which produces the permanent dilatation by stretching the inflamed and damaged walls which have lost their normal elasticity (McLean, 1957c).

b. Effects on the Distal Passages

Here the situation is more complex. In the exudative phase of acute bronchiolitis, the formation of exudate in the inflamed bronchioles may exceed the capacity of the lymphatics within the walls to remove it, so that the excess may run into the distal passages and block the alveolar pores leading to air absorption and collapse. If bacterial infection spreads into the area consolidation results.

As the exudative phase passes the exudate may be resorbed and re-aeration follow; at this stage, expulsion of the plug becomes possible, but, as in simple bronchiolitis, this does not necessarily occur and a proportion of the inflamed bronchioles may be obliterated.

On the other hand, without re-aeration, the plugs cannot be expelled and bronchiolar obliteration will result if this circumstance persists unchanged; the longer collateral ventilation is abolished, the longer bronchiolar infection persists and the greater proportion of bronchioles are obliterated. This is illustrated by the observation that once a lobe has been collapsed for six weeks, bronchiectasis can be anticipated, even if re-aeration occurs subsequently.

It is therefore necessary to consider the two situations which exist after the exudative phase of respiratory inflammation: where the distal passages are aerated, and where they are non-aerated.

(i) *Distal Passages Aerated*

It is primarily the clinically milder respiratory infections that lead to bronchiolar obliteration with normally aerated air passages distally. These infections include both simple acute bronchiolitis (the " acute bronchitis " of the clinician) and the milder forms of viral pneumonia and bronchopneumonia. Since aeration and, therefore, collateral ventilation are either not affected or are soon re-established, the proportion of inflamed bronchioles that become obliterated is usually very small indeed. Thus, only after repeated incidents (particularly if they are prolonged for any reason) will the proportion of bronchioles obliterated become high enough to interfere with normal lung function (McLean, 1957c).

In the healthy adult this requires at least three-quarters of all bronchioles obstructed; when this figure is exceeded the phenomenon of " air-trapping " occurs in the sequestered, collaterally ventilated parts of the lung. This has been demonstrated experimentally, and the great increase on coughing of the pressure gradient between the affected parts and normal lung noted (Baarsma, Dirken and Huizinga, 1948).

It is this disruptive force acting on distal air passages beyond obstructed and inflamed respiratory bronchioles which is assumed to be the basic cause of pulmonary emphysema (McLean, 1957b, c). Temporary " air-trapping " may occur during any respiratory infection (because of considerable bronchiolar obstruction by mucus and exudate), but, more significantly, if the proportion of bronchioles permanently obliterated as a result of previous infections becomes significant in itself, " air-trapping " may exist indefinitely, being reduced only by the improvement in collateral ventilation resulting from dilation and breakdown of the walls of the distal passages involved.

This change, emphysema, first affects those passages just beyond the usual site of bronchiolar obstruction (McLean, 1957b). These passages, the second and third order respiratory bronchioles, are near the middle of the secondary lobules, so that the initial lesion in emphysema of the slowly progressive variety is centrilobular. The breakdown of the walls of these passages establishes new communications and collateral ventilation is much improved, with the result that trapping is reduced. In one sense, therefore, the early lesion of emphysema is compensatory, since air-trapping is ameliorated without excessive destruction of lung tissue (McLean, 1957b).

As these changes progress with further infections and further bronchiolar obliteration, the whole lobule becomes involved (McLean, 1957c). With increasing destruction of lung tissue, bronchiolar collapse on forceful expiration (including coughing) appears, presumably because of the loss of tissues supporting the bronchiole (Dayman, 1951). This is manifest by a reduced rate of air flow during expiration and, more significantly, by a sharp reduction in the maximal velocity of air-flow in coughing (Barach, 1955). Subsequent infections last longer and advance the rate of evolution of the disease.

Emphysema is therefore seen, typically, to be the end result of repeated mild respiratory infections. Most people die before emphysema is sufficiently advanced to be evident clinically, but few elderly people have no macroscopic morphological evidence of the disease (McLean, 1956a). Certain factors can be recognized which accelerate the evolution of emphysema (McLean, 1957c). Among these, two important factors are polluted atmospheres and smoking;

both increase mucus secretion and prolong the bacterial phase of respiratory infections. Even in normal persons these chemical irritants may induce sufficient hypersecretion of mucus to overload the ciliary mechanism and so produce a chronic cough, but once emphysema has reached the clinical level (or earlier if hypersecretion is considerable), the efficacy of the cough mechanism becomes so defective that prolonged bacterial bronchiolitis occurs, establishing the purulent phase " chronic bronchitis," so prominent a precursor of *clinical* emphysema in Britain.

(ii) *Distal Air Passages Non-aerated.*

Permanent non-aeration of the distal air passages is seen in two forms. The first is the chronically contracted, fibrotic lobe; this has been considered in the section dealing with bronchiectasis, since such lesions present clinically as bronchiectasis.

The second follows involvement of smaller lung units, each individual lesion necessarily arising originally from simultaneous obstruction of the supplying bronchus or bronchiole and occlusion of the alveolar pores, thus cutting off both direct and collateral ventilation from the affected part; air absorption and collapse follow.

Such lesions may be localised or diffuse (McLean, 1956a). Localised pulmonary " scars," representing what was originally a much larger volume of lung tissue, are exceedingly common, and in these scars it is often easy to demonstrate obliterated bronchiolar remnants (Fig. 7).

Diffuse " scarring " or diffuse pulmonary fibrosis may also result from the commoner infections. Diffuse patchy collapse is a common radiological finding in the more severe clinical respiratory infections, especially those viral infections in which there is no super-infection with virulent bacteria to invade the exudate in the distal passages and lead to consolidation rather than collapse. On recovery from the acute phase of these infections, some or many of these non-aerated regions may not resolve and bronchiolar obliteration will occur generally in these areas. At the same time the aerated regions will be recovering from severe and prolonged bronchiolitis, and bronchiolar obliteration will be likely to have occurred to a considerable extent, resulting in some degree of emphysema in the remainder of the lung.

In this manner a full range of intermediates between classical emphysema and classical diffuse fibrosis may arise, depending on the nature and severity of the inflammatory episodes causing the lung damage. Whereas classical emphysema is generally the result of repeated relatively mild episodes, a similar degree of bronchiolar obliteration may be produced by a single severe incident in which involvement of the distal passages occurs widely and does not resolve. The end result is a diffusely " scarred " emphysematous lung.

In conclusion, this study has been restricted to the consideration of the commoner agents producing respiratory inflammation, and has not included other causes of chronic lung disease, such as tuberculosis or pneumokoniosis. In these conditions the damaging agents have considerably different properties from those which are discussed here, particularly in their chronicity; yet in them bronchiolar lesions are as important as they are neglected. Moreover, since each can produce extensive bronchiolar obliteration, all three morphological forms of chronic lung disease may result, with their attendant defects in homeostasis, and therefore liability to further bronchiolar damage from all types of inflammatory involvement.

Summary

A plea is made for the re-examination of the natural history of non-specific chronic lung disease from the viewpoint of bronchiolar pathology.

This entails first an appreciation of the normal structure and function of the bronchial tree in general, and of the small bronchioles in particular.

Summarising previous work, it is concluded that in the commoner form of respiratory tract inflammation, the bronchiolar element, acute bronchiolitis, is the significant lesion and warrants closer attention than has been given it in the past.

Permanent damage following acute bronchiolitis is extremely common, the most important sequel being bronchiolar obliteration. Some degree of diffuse bronchiolar damage, including obliteration, has been demonstrated in all adult lungs examined.

Non-specific chronic lung disease is divided into three main morphological forms: bronchiectasis, emphysema and pulmonary fibrosis. In all three forms bronchiolar damage and obliteration is extreme. Bronchiolar obliteration is regarded as the essential lesion in the pathogenesis of these conditions, the severity of the chronic lung disease being satisfyingly related to the operation of factors acting to produce long-standing bronchiolar obstruction and, therefore, obliteration.

The operation of other factors determines which of the three morphological forms will predominate, and clinically, which diagnosis will be made. In this manner the natural history of chronic lung disease can be examined as a whole, stressing the essential unity of its three morphological forms.

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PULMONARY OEDEMA

By Samuel Oram

King's College Hospital, London

In 1834 Laennec defined pulmonary œdema as " infiltration of serum into the substance of the lung to such a degree that in respiration its permeability to the air is diminished."

The unique structure of the substance of the lung, consisting as it does of thin walls containing blood vessels, gives œdema of the lungs a special character. Namely, if the serum in the interstitial lung tissue cannot be carried away quickly enough by the lymphatics it immediately pours into the alveolar lumina and, to a lesser extent, into the pleural cavities. James Hope (1832) was probably the first to realise that engorgement of the lungs was the cause of cardiac asthma.

Ætiology

A surprisingly large number of clinical conditions can give rise to pulmonary œdema, but the commonest organ at fault is the heart. A clinical classification which I have found useful is as follows:

1. *Cardiac.* (i) Left ventricular failure—hypertension, coronary artery disease, aortic stenosis and incompetence, mitral incompetence, and acute rheumatic carditis.
    - (ii) Mitral stenosis.
    - (iii) Intravenous infusions.
    - (iv) Congenital heart disease where a shunt is present—patent ductus arteriosus, auricular septal defect, and ventricular septal defect.
    - (v) Acute and chronic cor pulmonale.
2. *Cerebral lesions*, including trauma.
3. *Pulmonary lesions*, including trauma.
4. *General causes*—shock, allergy, hollow viscera stimulation, drugs (iodides, morphia, thiouracils, prostigmine, insulin), thyroid crises and burns.

Hypertension is the commonest cause of acute left ventricular failure and pulmonary œdema, and compared with it mitral stenosis is an uncommon cause. All forms of hypertension can give rise to pulmonary œdema, benign and malignant, coarctation of the aorta, and as a result of a phæochromocytoma of the adrenal medulla. Uræmia as a result of chronic nephritis is often accompanied by attacks, and in a few cases there may be little or no acidosis, the only evidence of renal failure being a moderate rise in blood urea. Toxæmia of pregnancy can also be complicated by pulmonary œdema.

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Mitral stenosis has become an extremely important cause of pulmonary œdema, in view of the excellent results of valvotomy in this type of case. It is not failure of the left ventricle as the obstruction is, of course, proximal to that chamber. The syndrome of " pulmonary apoplexy," in which these patients cough up large amounts of pure blood, has a similar mechanical origin.

If the left ventricle is largely destroyed by a cardiac infarct then pulmonary œdema is to be expected, but I have encountered several patients in whom the cardiographic changes and coronary episodes may be minimal and yet pulmonary œdema, sometimes of the subacute type, may result. Occasionally acute pulmonary œdema occurs as the first symptom in a previously healthy person as a result of a cardiac infarct, and yet little or no pain may accompany the episodes. It may well be, of course, that the frightening dyspnœa tends to render the patient less aware of pain. Such a cause for acute pulmonary œdema should be particularly suspected if the patient is male, middle-aged or over, if the blood pressure falls during the attack and no history of previous dyspnœa on effort can be obtained.

According to Luisada and Cardi (1956) it is not sufficiently realised that acute pulmonary embolism may at times give rise to pulmonary œdema, and I have more than once seen the typical blotchy shadows of pulmonary œdema (see below) erroneously reported as pulmonary infarcts radiologically. It is possible that occlusion of an important branch of the pulmonary artery causes increased flow in the other branches with production of a high capillary pressure.

In chronic cor pulmonale the hypoxia favours the production of œdema, especially if there is no destruction of capillaries. Luisada and Cardi are of the opinion that if much lung tissue is destroyed by patchy fibrosis or emphysema, then an increase in venous return may tax the already distended vessels in the relatively normal areas and produce pulmonary œdema. Chapman *et al.* (1939) have described acute pulmonary œdema associated with chest deformity.

Acute pulmonary œdema is a well-known danger of intravenous infusion, particularly if the amount is too great or the infusion is given too rapidly. If the blood volume is already increased, as in high-output states such as chronic anæmia or pregnancy, the danger is all the greater.

Damage to the brain can result in pulmonary œdema, both in the experimental animal and in man. Clinically, not only may injury to the skull produce flooding of the lungs, but cerebral hæmorrhage, embolism and thrombosis, and even subarachnoid hæmorrhage, may at times be complicated by it. In children as well as adults the association of meningitis, encephalitis, poliomyelitis and cerebral tumour or abscess with pulmonary œdema is well recognised.

Local lesions of the lung may give rise to acute pulmonary œdema, although not commonly. " Traumatic wet lung " is of particular interest because of the tendency of the œdema to spread from the damaged to intact areas of the lung, but its exact causation is still unknown. Although subacute pulmonary œdema may simulate pneumonia, and vice versa, one may also predispose to the other. Influenzal bronchopneumonia is especially liable to pulmonary œdema. Drowning, strangulation and asphyxia, and, of course, the inhalation of irritant gases, including those used in warfare, all may cause pulmonary œdema. It may also arise suddenly if thoracocentesis is performed too rapidly, and it occasionally occurs after lobectomy.

General causes of acute pulmonary œdema are not common. Among allergic causes may be mentioned angioneurotic œdema, serum sickness, or sensitivity to penicillin, particularly if administered by inhalation. Too rapid paracentesis abdominis or decompression of the bladder, insulin shock and burns may all cause it, too. Shock is frequently associated with pulmonary œdema, but at times they both have a common cause. The cardiogenic shock in cardiac infarction is particularly prone to this complication.

PHYSIOPATHOGENESIS

Since the advent of cardiac catheterisation our understanding of the mode of production of pulmonary œdema has increased, and the occurrence of actual attacks during the course of cardiac catheterisation has enabled circulatory changes to be studied in the human lung. Most writers have attempted to evolve one theory to apply to all cases, but it is likely that different mechanisms predominate. Although the exact pathogenesis is still not clear in many cases, there are three factors of prime importance, namely, a raised pulmonary capillary pressure, increased permeability of the pulmonary capillaries, and decreased osmotic pressure of the blood. Other factors which are less well understood are the role of sympathetic stimulation leading to displacement of a large mass of blood from the periphery to the lungs, endocrine factors and the significance of locally elaborated humoral agents such as serotonin. The pulmonary capillary pressure is that pressure recorded by a cardiac catheter wedged as far as it will go into the finest branches of the pulmonary artery (" wedge pressure "). It reflects well the pressure changes not only in the pulmonary veins themselves but in the more distal left atrium (Epps and Adler, 1953). The normal figure is between 5 and 10 mm. Hg. When the plasma proteins are normal, namely 7-8 G. per cent., the osmotic pressure in the pulmonary capillaries is 25-30 mm. Hg, but the effective osmotic pressure is certainly less, as the lymph in the lungs has a high protein content, and the true figure is almost certainly less than 20 mm. Hg. If the filtration pressure in the pulmonary capillaries exceeds the effective plasma osmotic pressure, or if the permeability of the capillaries is increased, then fluid will pass through the capillary wall into the interstitial tissues of the lung. There is, however, a protective measure in that if the pulmonary arteriolar resistance is very high œdema of the lungs will not occur. By collating published records and adding his own, Hayward (1955) found that in mitral stenotics before attacks of pulmonary œdema the pulmonary capillary pressure was raised to between 25 and 30 mm. Hg, and during the attack it rose to between 32 and 54 mm. Hg. The pattern was similar in acute pulmonary œdema due to left ventricular failure. Although changes in pulmonary arteriolar resistance during the attacks were variable, no example occurred in those patients with a very high resistance.

Pulmonary œdema following cardiac infarction, hypertension or aortic valve disease results from a sudden decrease in the power of the left ventricle with resultant severe increase in left auricular and pulmonary capillary pressure. However, as pointed out by Luisada and Cardi (1956), the raised pulmonary capillary pressure will only persist if there is an adequate venous return, and this may account for the fact that in extremely severe cases of cardiac infarction pulmonary œdema is less common than in less severe cases. A second feature which militates against recovery in these patients is the accompanying peripheral vasoconstriction. This causes both an increase in arterial resistance, against which the already damaged left ventricle has to work, and an increase in the venous return to the right heart, both of which result in the production of a high capillary pressure. Peripheral vasoconstriction in cardiac infarction may well be initiated by cerebral anæmia or by the effect of hypotension on the carotid sinus or hypoxia on the carotid body. The peripheral effect of serotonin liberated by the infarcted muscle is as yet uncertain. Another factor which has been suggested as leading to a rise in pulmonary capillary pressure is active contraction of the pulmonary veins (Burch and Romney, 1954)—the so-called "pulmonary venous throttle mechanism," and it is interesting to note that de Bettencourt *et al.* (1953) have shown by tomography that the pulmonary veins in such patients are frequently smaller than normal.

In patients with left ventricular failure, even gentle exercise will cause the pulmonary capillary pressure to exceed the effective plasma osmotic pressure, so that interstitial œdema will result, and it is probably because the lymphatics in this early stage are able to remove this serum before it enters the alveoli that dyspnœa in these patients may be unaccompanied by any signs of moisture in the lungs, although the chest X-ray may at that stage show an increase in hilar shadows, and mercurial diuretics effectively improve the patient's dyspnœa.

The factors responsible for the high pulmonary capillary pressure in mitral stenosis have been described by Gorlin *et al.* (1951). They have shown that in order to maintain the cardiac output in the presence of severe obstruction at the mitral valve a high left atrial pressure is necessary. Tachycardia with its shortened diastole will impair the emptying of the left auricle and will shorten the diastolic filling period of the left ventricle, rendering necessary a higher pressure gradient across the mitral valve. It is well known that tachycardia induced by exertion, nervousness, excitement, exposure to cold or infection may precipitate an acute attack in mitral stenotics.

The amount of blood in the pulmonary capillaries is normally only about 50-60 ml. (Roughton, 1945), and Ball *et al.* (1952) have pointed out that the left auricle and pulmonary veins are relatively inelastic and that, therefore, changes in pulmonary capillary pressure may be brought about by only a slight increase in the pulmonary blood volume. This may well explain the clinical, and radiological (Jackson, 1951), observation that patients with mitral stenosis accompanied by acute pulmonary œdema usually have only slight to moderate enlargement of the left auricle, and in those patients with very large left auricles it is probably because large volume changes are possible with little alteration in pressure that they are protected from such episodes.

The mechanism of production of acute pulmonary œdema as a result of intravenous infusion is probably very similar to the above, but additional factors are the increased volume of blood in the lungs and the lowered osmotic pressure. Similarly, in uræmic patients the decreased osmotic pressure in nephrotics must play an important part, and the retention of metabolites in nephritics would be expected to increase the capillary permeability. The increase in capillary permeability as a result of damage to the endothelium from toxic gases is the most important factor in this type of patient, and it is interesting that pulmonary œdema induced by inhalation of phosgene is not associated with pulmonary hypertension (Patt *et al.*, 1946). "Neurogenic" pulmonary œdema has been produced in animals by the injection of fibrinogen and thrombin into the cisterna magna by Cameron (1948). Division of the vagi reduced or prevented the œdema, which is presumably of reflex origin and probably results from disturbance of intracranial pressure. Lesions of the central nervous system result in central stimulation of the sympathetic nervous system, which causes reflex vasoconstriction. This in turn increases the load on the left ventricle and is also thought to lead to redistribution of blood and its accumulation in the lungs.

CLINICAL FEATURES

Clinically, pulmonary œdema may range widely in severity. It is often acute enough to warrant James Hope's term "cardiac asthma," and sometimes the attack may be fulminating. On the other hand, it may be so slight as to be evidenced only by dyspnœa on exertion, with or without occasional orthopnœa. These patients may often be diagnosed in error as chronic bronchitics. It is only recently that a subacute group has been recognised, and its clinical importance lies in the fact that, although there may be intense dyspnœa, the lungs may show no abnormality on auscultation, and this is in striking contrast to the extent of the shadows seen radiologically. Another characteristic feature of the subacute examples is that the exudate is apt to clot and become organised, and at autopsy the lungs may have a rubbery feel. The histological changes, consisting essentially of infiltration of the intra-alveolar exudate with mononuclear cells and fibroblasts, have been described by Hadfield (1938) and Doniach (1947). Among such causes are malignant hypertension, acute nephritis, uræmia, polyarteritis nodosa and the so-called "rheumatic pneumonia."

Attacks are particularly apt to occur at night, and if the orthopnœic patient slips down in bed this is likely to increase his pulmonary congestion, and it may well be that the nightmare which commonly precedes these attacks induces tachycardia. It is also possible that sudden movement whilst asleep, following a period of muscle relaxation, may cause a sudden and appreciable increase in the venous return. In those patients who have their attacks during the day, excitement, fear, cold or exertion may all precipitate the paroxysm. It usually begins with restlessness and a feeling of tightness or actual pain across the front of the chest, and a short, non-productive cough appears. Breathing becomes more and more difficult and laboured, the patient feels suffocated and has to sit up, or even climbs out of bed and leans forward across a chair. Usually within a few minutes moist sounds can be heard in the chest, and if the œdema increases frothy sputum is produced; this is classically pink but not often so. It varies from a little to vast quantities such as several pints in an hour or two. There is usually much expiratory wheeze present in the chest at this stage. The patient's skin becomes cold and clammy, white and cyanotic, his lips are dark and he may vomit, but cyanosis in the early stage or in short attacks is rarely severe, and when present at first is peripheral in type, but during the frothing stage it becomes central. The blood pressure may either increase or fall, and the pulse becomes correspondingly of greater or diminished volume. Luisada and Cardi (1956) have drawn attention to these two types of patient which may require different treatment (see Table). Examination of the chest during an attack reveals laboured breathing, a resonant percussion note, and usually fine râles over the entire chest, unless they are obscured by coarser moist sounds produced by foam in the trachea and bronchi. Tachycardia is invariable and the neck veins are engorged. The temperature is usually normal during the attack but may be a little low if much shock is present. It commonly rises soon after the attack owing to the reabsorption of altered protein from the lung.

TABLE I.—CLINICAL TYPES OF ACUTE PULMONARY OEDEMA

	Group I	*Group II*
Frequency	Common	Less common, but increasing.
Main causes	Hypertensive heart disease	Cardiac infarction.
	Mitral stenosis	
	Aortic incompetence	Aortic stenosis.
	Intravenous infusions	Pulmonary embolism.
Blood pressure	Increased usually	No change, or lowered.
Pulse	Full	Small.
Shock	Absent	Often present.
Reduction of venous return ..	Beneficial	May be harmful.

RADIOGRAPHIC APPEARANCES

These may be diagnostic. Not every patient with cardiac paroxysmal dyspnœa shows radiological changes, especially if the attack is mild, but on the other hand the changes are frequently evanescent and may be gone in a few hours. Typically, acute pulmonary œdema shows the so-called " bat-wing " or " butterfly " appearance, but the appearance is commonly asymmetrical. The dense cloudy opacities cover both hilar regions and, characteristically, leave a clear zone beyond this so that the apices above and the costophrenic angles below and the periphery remain clear, giving a continuous light outer zone (Fig. 1). Less commonly the opacities affect mainly the hilar region and softer irregular blotches lie farther out towards the periphery. According to

Jackson (1951) hydrothorax is unusual in uncomplicated acute pulmonary œdema, and large effusions are seldom seen unless congestive heart failure is also present. However, smaller collections of fluid in the posterior costophrenic angle, requiring a lateral or oblique film for their detection, are more common (Lenègre and Minkowski, 1946). The interlobar fissures are commonly thickened, especially on the right side. Almost always the shadows are bilateral, and when one lung is more affected than the other it is usually the right (Zdansky, 1933). The lung fields sometimes clear within one to three days, and usually within a week, and this is often of great help in distinguishing the radiological appearance from other conditions. They tend to clear quicker in pulmonary œdema due to mitral stenosis than left ventricular failure (Fig. 2). Short (1956) has pointed out that it is rare to find radiological changes of acute pulmonary œdema in patients with mitral stenosis if the left auricle is very large, and that it is commoner in patients with normal rhythm and in pregnancy. Short horizontal lines may be seen in the costophrenic angles both in severe mitral stenosis and in left ventricular failure, and were first described by Kerley (1933). According to Grainger *et al.* (1955), this appearance is due to lymphatic distension and interstitial œdema in the peripheral interlobular pulmonary septa. It is probable that thickening of the alveolar basement membrane prevents the easy passage of the œdema fluid into the alveoli, as shown by Parker and Weiss (1936).

TREATMENT

As well as dealing with the acute attacks, preventive measures can be taken to avoid them.

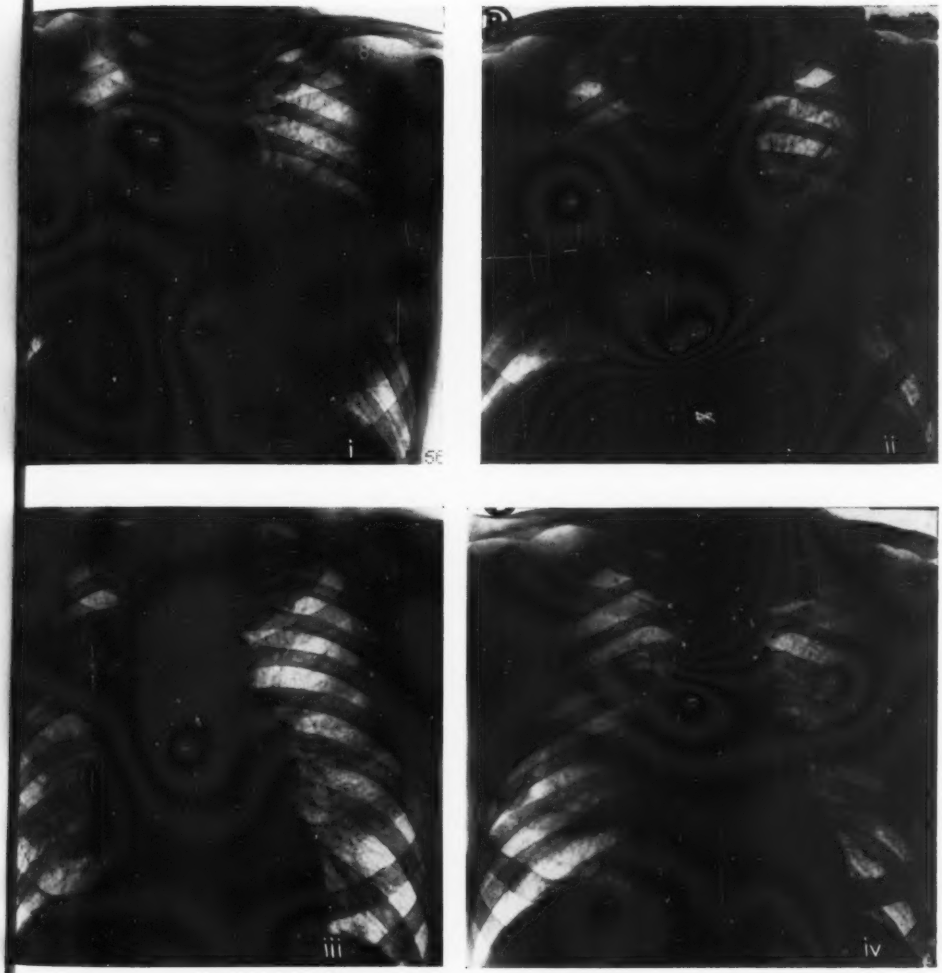
The Acute Attack

Both drugs and physico-chemical methods may be employed.

Drug Therapy. Many drugs have been used in treatment, but only those of proven clinical value will be discussed.

Morphine will terminate most attacks and is the drug of choice in attacks due to hypertension, cardiac infarct, uræmia and mitral stenosis, but it must be remembered that large doses of morphine in cardiac infarction may increase the shock, and great caution is necessary in cerebral lesions and in chronic cor pulmonale. Its effect on the fœtus in pregnancy must be remembered too. Usually ⅓–¼ gr. is given subcutaneously, but if the attack is fulminating ⅙ gr. can be given slowly intravenously, but it is then more liable to cause vomiting. Its action in pulmonary œdema is not fully understood, and it is commonly thought that it helps to depress harmful pulmonary vasomotor reflexes. It apparently causes no change in cardiovascular dynamics (Altschule, 1954) and extremely large doses are needed to affect the pulmonary vessels (Luisada, 1928). The pressure in the pulmonary artery of cardiac patients is usually decreased but may be increased (Scébat and Lenègre, 1949). It may well be that it helps to lower the pulmonary capillary pressure by decreasing anxiety, reducing the muscular movements which cause an increase in the venous

PLATE XVI



1.—Male, aged 46. Acute pulmonary oedema as a result of hypertension. (i) 20.5.56. Bilateral but mmetrical clouding of lung fields with apices and costophrenic angles remaining clear. (ii) 21.5.56. Within hours considerable clearing of the lung fields has taken place. (iii) 23.5.56. On the fourth day the left lung is clear. (iv) 28.5.56. Within eight days both lung fields are normal.

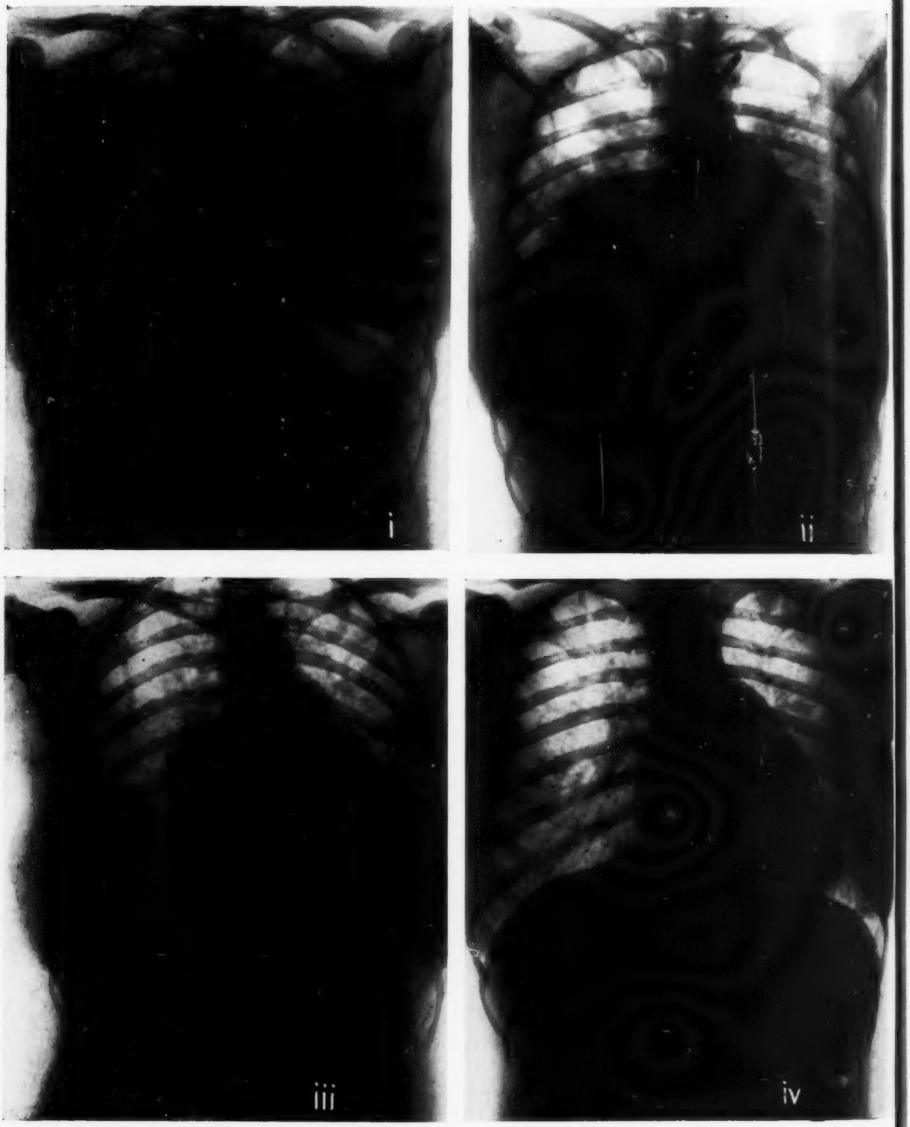


FIG. 2.—Female, aged 32. Acute pulmonary oedema from mitral stenosis. (i) 31.10.55. Such gros clouding of both lung fields is present, including the costrophrenic angles, that the cardiac silhouette i completely obscured. (ii) 1.11.55. By the next day considerable clearing has taken place and the lef cardiac border can be distinguished. (iii) 3.11.55. Further clearing has occurred, particularly of th right lung. (iv) 8.11.55. Within eight days both lung fields are normal.

return to the heart, and depressing the metabolic rate which will lower the oxygen requirement of the tissues and hence help to lower the cardiac output. By depressing the respiratory centre it may decrease the suction effect of dyspnœa.

Atropine $\frac{1}{60}$-$\frac{1}{100}$ gr. has been given for many years in this country and it is usually combined with morphine. Its " drying " action is probably negligible and the tachycardia which it induces may be actually detrimental. It is doubtful whether it is of value unless bradycardia is present, as in cerebrovascular lesions and some cardiac patients. In view of the atropine-like action of pethidine this drug should not be substituted for morphine.

Aminophylline (theophylline ethylene-diamine) stimulates ventricular contraction (Starr *et al.*, 1937) and causes coronary and peripheral vasodilatation. It is also a bronchodilator and a weak diuretic. Its main disadvantage in acute pulmonary œdema would appear to be stimulation of the respiratory centre, and in acute cardiac infarction excessive stimulation of the myocardium may cause death (Merrill, 1943). Luisada (1928) considers that the stimulant effect on the respiratory centre is so harmful that its routine use cannot be recommended, but few clinicians would agree with such severe condemnation. It will certainly stop Cheyne-Stokes respiration within a minute or two if given intravenously; the dose is 0·25 to 0·5 G. given very slowly in 20 ml. of distilled water.

Mercurial diuretics are of little immediate value in the acute attack, but should always be given, as they will cause a considerable fall in pressure in the right auricle and right ventricle within half an hour (Scébat *et al.*, 1949) if given intravenously. However, intravenous Mersalyl, 1 ml., is only justified in the most acute cases. In all other patients it should be given intramuscularly.

Digitalis must be used with caution. It is of most value when the patient has auricular fibrillation with a rapid ventricular rate. It would seem to have an obvious place in treatment in view of its ability to increase the efficiency and emptying of the failing left ventricle, but if given intravenously it may cause a rise in blood pressure and actually lead to acute left ventricular failure (Bayliss *et al.*, 1950). For this reason it is best given orally. Another risk of intravenous digitalis in the presence of cardiac infarction is the production of ventricular tachycardia and fibrillation as a result of excessive irritability of the hypoxic myocardium. The employment of digitalis presupposes that the damaged left ventricular wall can still be stimulated and that the right ventricle will not be unduly stimulated, so that no further rise of pressure in the pulmonary artery will result. Intravenous digitalis may lower the venous pressure rapidly. In mitral stenotics, if given intravenously it may prove dangerous and even precipitate acute pulmonary œdema, as shown so strikingly by Lenègre and Scébat (1952). In these patients the high right ventricular output is responsible for the raised pulmonary capillary pressure, and digitalis may cause the right ventricular output to increase still further whilst the outflow from the lungs is impeded by the mitral obstruction (Haring and Luisada, 1953).

Since it was realised that sympathetic inhibition, either by stellate ganglionectomy (Pierach and Stotz, 1952) or spinal anæsthesia (Sarnoff and Farr, 1944) was beneficial in some patients suffering from acute pulmonary œdema, drugs with a similar ganglion blocking action have been tried, including hexamethonium compounds and mecamylamine. In hypertensive left ventricular failure reduction of blood pressure by ganglion blocking drugs given parenterally may give dramatic relief, presumably by lowering peripheral resistance and relieving the left ventricle (Smirk, 1954). Either hexamethonium bromide (Vegolysen) 20 to 30 mg. or pentolinium tartrate (Ansolysen) 5 mg. subcutaneously should be given. Although Ellestad and Olson (1956) obtained good results in acute pulmonary œdema in some patients with a normal blood pressure, these are almost certainly contraindicated if the blood pressure is low, and certainly if peripheral circulatory failure is present. There seems no doubt that they can lower the pressure in the pulmonary artery (Fowler *et al.*, 1950) but their effect on the cardiac output is less certain. Some workers have found an increase in cardiac output (Davies *et al.*, 1954), others a decrease (Storstein and Tveten, 1954), and others no change (Gilmore *et al.*, 1952). In very tight mitral stenosis the patient may be unable to increase his cardiac output and is dependent on severe peripheral vasoconstriction to maintain his venous return; in such a patient peripheral vasodilatation and further reduction of blood pressure might cause a disastrous fall in the central venous filling pressure.

Although it is still uncertain whether histamine is liberated in acute œdema of the lungs, antihistaminic drugs seem worth a trial if only for their depressive action on the central nervous system.

Physico-chemical Methods. If the patient is not already upright in bed he should be immediately propped up with his legs dependent over the edge of the bed, or ideally he should be nursed in a cardiac bed. If he is drowning in œdema fluid a suction catheter should be inserted down the trachea, either through the nose or mouth, and a mechanical aspirator may be used if available.

Provided the blood pressure is not diminished, venesection or the application of tourniquets may prove extremely beneficial as an emergency measure. At least a pint should be withdrawn rapidly from an antecubital vein, or tourniquets are applied to all four limbs and inflated to 50 mm. Hg at a pressure sufficient to obstruct the venous return. They should be released slowly every twenty minutes to avoid venous thrombosis. They are particularly effective in hypertensive patients, in those suffering from aortic incompetence, and in some cases of mitral stenosis with a high venous pressure.

Oxygen is beneficial to all patients and can be best administered by means of a very light disposable plastic mask (British Oxygen Company), but foam in the bronchioles prevents it reaching many alveoli. High concentrations of oxygen are irritant, so its administration should be intermittent.

The frothy character of the œdema fluid is due to its high protein content of 2·5-3 G. per cent. (Drinker, 1945), and it has been suggested that fine foam in the air passages may by itself be responsible for continuation of the attack by interfering with the normal exchange of gases with resultant anoxia, which in turn increases the permeability of the capillaries. If the surface tension of the bubbles can be reduced they burst, and the fluid composing them then occupies a much smaller volume. Various de-foaming agents have been tried, such as ether, alcohols and silicones, or combinations of these. A simple method which gave very promising results (Luisada *et al.*, 1952) was to use a nasal catheter and a 95 per cent. solution of ethyl alcohol. The alcohol is placed in the usual humidifier bottle. For the first few minutes the flow of oxygen is kept to 2 to 3 litres a minute, then, when the patient's mucosæ become adapted to the irritant gas, the rate of flow is gradually increased to 9 or 10 litres a minute. After about 40 minutes a rest period of 10 minutes is instituted to prevent systemic effects due to excessive absorption of alcohol. The results of treating 50 attacks by this method have been summarised by Goldman and Luisada (1952). Whatever the cause of the pulmonary œdema, such anti-foaming therapy might well be instituted immediately whilst a clinical assessment is being made to determine other therapy.

Positive pressure respiration has been advocated on the theoretical basis that increased pressure in the alveoli counteracts the high pulmonary capillary pressure and thus decreases transudation. Barach *et al.* (1938) advised breathing against the positive pressure of 3 to 6 cm. water, and it was later found to be particularly indicated in warfare gas poisoning by Barach (1944).

Spinal anæsthesia was tried by Sarnoff and Farr (1944) in patients refractory to other methods of treatment. Its mechanisms and indications are similar to those applying to sympatholytic drugs, as its action is to induce an intense vasodilatation and thus decrease the venous return to the right heart and lower the pulmonary artery pressure.

Preventive Measures

Intravenous infusions of blood, plasma or saline should be given with particular caution in patients with an already increased blood volume, such as in the chronically anæmic or pregnant, and rapid or large infusions should be avoided in the elderly.

Hypertensive patients should be encouraged to sleep well propped up at night, and the nightly use of a sedative together with digitalis, fluid and sodium restriction and antihypertensive drugs will often prevent attacks. A rectal suppository of aminophylline, 0·4 G., will often prevent the patient being awakened by dyspnœa.

Mitral valvotomy is effective in preventing attacks of acute pulmonary œdema in mitral stenotics, and in such patients it is important to realise that these attacks may be either fatal or of very transient duration, lasting a few hours only, and between times the patient may have very little exertional dyspnœa and little or no overall cardiac enlargement radiologically. Immediately after valvotomy the left auricular pressure is lowered, often to normal (Munnell and Lam, 1951), and the congested lung can be seen to improve at operation immediately the mitral valve has been split.

From what has been said previously it is obvious that the slow removal of effusions from the pleural sac, pericardium or peritoneal cavity is indicated, and a distended bladder should always be decompressed slowly.

Summary

Acute pulmonary œdema is encountered in a great variety of patients, the commonest of which have cardiac disease, usually left ventricular failure or mitral stenosis. The severity may vary from fulminating to chronic. Two types of patient may be recognised, namely those with a high blood pressure and full pulse, and those with a low blood pressure, poor pulse and a tendency to shock.

The exact mechanism of the production of pulmonary œdema is still uncertain, but a high pulmonary capillary pressure, increased permeability of the pulmonary capillaries and a decrease in the osmotic pressure are the most important features. The level of the pulmonary capillary pressure in both left ventricular failure and mitral stenosis always exceeds the effective osmotic pressure of the plasma.

Emergency treatment is to prop the patient as upright as possible and if necessary insert a suction catheter down the trachea. Other useful agents in treatment are morphine, aminophylline, venesection, oxygen and mercurial diuretics. Digitalis should be used with caution. De-foaming agents are simple to use and seem worthy of further trial. Before using any particular method of treatment it should be determined whether a reduction in venous return is likely to prove beneficial, for example in patients with a raised blood pressure, or harmful, as in those with a low blood pressure and tendency to shock.

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THE TREATMENT OF PATIENTS WITH SEVERE ASTHMA AND CHRONIC BRONCHITIS

A. G. Ogilvie

From the Royal Victoria Infirmary, Newcastle-upon-Tyne

It is considered that asthmatics are peculiarly liable to develop chronic bronchitis, and the experience of a recent community survey in Newcastle (1957) gave very strong confirmatory evidence of this. Of 464 confirmed bronchitics, 43 were found to be asthmatical, whereas of 485 confirmed non-bronchitics selected by a random method, only 5 were asthmatics.

The use of such a term as " asthmatic bronchitis " has, however, been avoided as inaccurate and likely to prove misleading.

All the patients were severely disabled, losing at least three months' work each year, and in fact many had not worked for a number of years because of their disability. A number who were working for a considerable part of the year were able to do so only because they had managed to obtain very light work where they could " take their own time."

All were admitted in a deliberate attempt to improve their health. Emergency cases, such as status asthmaticus and acute infective episodes, were excluded. The series is otherwise unselected and consecutive. Diagnosis depended upon the clinical signs and upon the history. The clinical signs insisted on were poor air entry and expiratory obstruction, associated with an obvious bronchial stridor (though other signs were often present).

The history has not necessarily been uniform and the cases have, in fact, fallen into three groups.

In the first of these groups, a characteristic story of intermittent asthma from childhood became complicated at some point by persistent cough with sputum. Coincidentally continuous wheezing with breathlessness replaced the earlier intermittent asthmatic attacks. Recurrent winter " colds on the chest " became a further regular complication.

In the second group continuous asthma and chronic bronchitis commenced almost simultaneously, although acute asthmatic attacks occurred in addition in some cases.

The third group was much the smallest. In these cases, chronic bronchitis had been present for some years before becoming complicated by asthma, continuous with or without acute attacks.

In both the second and third groups persistent nasal catarrh was an extremely common associated symptom.

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Throughout, severe "colds on the chest" have been a characteristic feature, as in most cases of chronic bronchitis.

Other allergic manifestations, and an allergic family history, have been frequently noted, but have not been regarded as essential for diagnosis.

Eosinophilia is so variable a feature that it is valueless as a diagnostic criterion.

The patients were all admitted during the years 1955 and 1956, although some of them had been treated previously, and some have been readmitted subsequently. Several have, in fact, been admitted four or five times.

TABLE I.—ASTHMA WITH CHRONIC BRONCHITIS

Decade	*Male*	*Female*	*Totals*
0-20	1	1	2
21-30	2	4	6
31-40	8	14	22
41-50	24	8	32
51-60	22	15	37
61-70	11	8	19
Over 70	2	0	2
TOTALS	70	50	120

Table I shows the age and sex structure of the cases. This proves nothing, but the concentration of cases in the fifth and sixth decades may be noted.

When the treatment of these cases was considered, it seemed clear that this would have to be directed in two channels: towards the chronic bronchial infection on the one hand, and the persistent asthmatic state on the other.

What was visualised was simply to ascertain the best way in which control of the disability might be achieved. It was realised that this might be temporary, and indeed probably would be. If there were a possibility of good temporary control in a high proportion of cases, the problem of long-term treatment would come up for serious attention.

The suppression of active infection was clearly the first step, and in this the information available regarding the bacteriology of chronic bronchitis was taken as the guide to the choice of antibiotic, rather than routine bacteriological reports on the sputum.

Mulder (1952, 1956) and his colleagues in Leiden have been studying the problem for some years. They have found that in Holland the *Hæmophilus influenzæ* is the dominant pathogen in these cases, being present in significant numbers in 84 per cent., and in pure culture in 50 per cent.

May (1952, 1953) has studied the problem on a research basis at the Institute for Diseases of the Chest in London, and has found a roughly similar picture, although in his experiences the pneumococcus occupied a rather more prominent position. He was, however, concerned to emphasise the variability in the prevalence of these organisms which may occur from time to time, and to contrast this with the constancy of the *Streptococcus viridans*, the non-hæmophylic streptococcus, *Neisseria catarrhalis*, and such organisms. These organisms were found to persist in numbers which varied little with the clinical condition of the patient, suggesting that they were regular "colonial" inhabitants of the bronchial tree. On the other hand, the pneumococcus, the hæmophilus and also the *Staphylococcus aureus* vary considerably with the clinical state. Often in pure culture, one or other of these organisms are found in great numbers during infective exacerbations, falling during the intervening periods. They would appear to be the pathogens of chronic bronchitis, the others usually having the role of mere saphrophytes.

Stuart-Harris (1953) studied mainly the pneumococcus and did not use selective media favouring the hæmophilus, but he found pneumococci predominating in 50 per cent. of cases.

A study of the effect of antibiotics made by Mulder *et al.* indicated that for the suppression of the acute exacerbations removal of the hæmophilus from the sputum was essential.

Stuart-Harris noted improvement with suppression of the pneumococcus by penicillin, however.

The conclusion of these independent studies of large series of cases over a period of years, by experts of great experience, is inescapable. The main pathogens in chronic bronchitis are the pneumococcus, the hæmophilus and the *Staphylococcus aureus*, and others are of minor importance.

It is of interest that May was first prompted to study the bacteriology of chronic bronchitis by the report by Howell (1951) that cultures of the sputum varied widely not only from case to case but from day to day, in the same cases.

May observed that the culture of organisms in the sputum of chronic bronchitis much resembled a "lucky dip," although he did not express himself in this way. Take your loopful from one portion of the specimen, and obtain a fine growth of *Micrococcus catarrhalis*. Take another loopful 2 or 3 cm. to the right, and an equally fine growth of pneumococcus rewards you.

Thus the thorough bacteriological investigation of a single specimen of sputum is a laborious and time-consuming task, not to be expected where routine work is being pushed through at high speed in response to demand.

The most reasonable course to pursue under these circumstances is, therefore, to treat all cases expecting to find that the exacerbation, or persistent activity of the infective process, is due to one or more of the three main pathogens previously mentioned. For it is a most impressive fact that all those giving special attention to the bacteriology of chronic bronchitis, working over years independently, should have come to the same broadly similar conclusion.

In this series, therefore, infective activity was treated first by penicillin in full dosage (500,000 units 6-hourly) with streptomycin (1 G.) daily for a minimum period of five days. This is calculated to suppress the pneumococcus and other penicillin-sensitive pathogens which may be present. Many resistant staphylococcal strains may be expected to yield to the streptomycin.

If this was unsuccessful, or only partially successful, a short course of chloromycetin was administered, as this is the only antibiotic which invariably kills the *Hæmophilus influenzæ*. The dose given was 500 mgm. 6-hourly for a maximum period of five days. This period is never exceeded in my wards, as a longer period of administration is regarded as potentially dangerous. Given in this way, however, no evidence of sensitivity has emerged, as judged by leucocyte counts and other evidence over a number of years.

Finally, any persisting activity was dealt with by erythromycin 600 mg. 6-hourly, as some staphylococci seem hard to satisfy.

TABLE II.—ASTHMA WITH CHRONIC BRONCHITIS
Control of Active Infection. 97 Cases

Antibiotic	*Numbers*		
Penicillin with streptomycin ..	97		
Chloromycetin ..		35	
Erythromycin ..			4*

*1 case failed to respond

Table II shows the results in the 97 cases in which infective activity was present at the time of admission. It will be seen that two-thirds of the cases responded to penicillin and streptomycin, and almost all of the remainder to chloromycetin. Only one of the remaining four did not respond to erythromycin.

The criteria of infective activity should be mentioned. They consisted of pyrexia having no other cause, or purulent sputum (or both).

TABLE III.—ASTHMA WITH CHRONIC BRONCHITIS

Pyrexia	69
No pyrexia	51
TOTAL	120
Sputum purulent	72
Sputum mucoid	48
TOTAL	120

Suppression of activity was considered to have occurred when both of these clinical features had been suppressed.

The control of infection is generally essential prior to treatment by any hormone, and the adrenal hormones are no exception to the rule—rather the contrary.

The course of antibiotic treatment, therefore, preceded any other treatment. When it appeared that infective activity was subdued for the time being, an exercise tolerance test was attempted if the patient was well enough, and the effect of three separate antispasmodics upon the expiratory function was tested.

This exercise tolerance test is one which has been found to give reliable results, although it is unorthodox in the sense that it is not used anywhere else, so far as is known. It consists of the recording of the best of three or more tests of the forced expiratory volume (0·75 sec.) and of the forced vital capacity, followed by a stepping test for 4 minutes, or the limits of the patient's ability to continue the test, whichever was the shorter. The repetition of the respiratory capacity test after the exercise was then recorded as before, and the results were compared.

It has been found that in normal subjects the forced expiratory volume and forced vital capacity are significantly (and often considerably) increased after the exercise, although it has not been practicable to establish any numerical range of values owing to individual variation.

When the second reading is equal to the first, or falls below it, the result is regarded as abnormal and due to defective breathing capacity. The endurance time is, of course, also taken, and a poor endurance time is also considered as additional evidence of respiratory inadequacy.

This investigation is described, not in an attempt to foist yet another respiratory test upon the long-suffering emphysematous population, but merely in order to explain how improvement was assessed in the present series.

It was not the sole criterion, as subjective evidence and physical capability of the patient in ordinary life was also taken into account.

Improvement when recorded has consisted of a definite change in all three criteria.

In addition to this, a series of drug tests, using certain standard antispasmodics, were carried out in each case. These consisted of estimations of the forced expiratory volume before, and at half-hourly, and later, hourly intervals, over a period of six hours after exhibition of the drug. It was hoped in this way to select those patients who would best respond to hormone treatment, and for this reason all patients were treated, irrespective of the results.

The drugs tested were adrenalin hydrochloride (1 in 1,000) by injection, aminophyllin in the form of Theodrox by mouth, and a new aerosol solution which we were then testing prior to introduction for general use.

This rather time-consuming procedure was found to be useless for its purpose. A number of patients showing no response to these antispasmodics responded very well to hormone treatment. Furthermore, in a number of cases the only effective antispasmodic was the new inhalant solution. It therefore seems clear that the use of a few standard drugs as a screening device for the selection of patients for hormone treatment is valueless, although of course a drug test carried out as described is a most helpful way of assessing its therapeutic value in an individual case.

All patients were, in fact, given hormone treatment, which proved effective in 86 out of the 120 cases.

ACTH was given in a dose of 40 mgm. either 12-hourly in the form of the gel, or on alternate days if the long-acting Cortico-depot product was used. This dosage was continued for five days (or for three doses of Cortico-depot). Prednisone was also given for five days, the dosage being 10 mgm. 6-hourly. Maintenance dosage in all cases was commenced at a level of 5 mgm. 6-hourly, and gradually reduced as appeared consistent with the maintenance of the original improvement until it became obvious that deterioration was occurring. The drug was then gradually " tailed off."

In a few cases in which Prednisone was ineffective, maintenance was carried out with ACTH in a dose of 20 mgm.

ACTH was always used initially except when, on account of age, or for any other reason, it was thought to be unsuitable.

Of 96 cases, ACTH produced a striking and satisfactory improvement in 61.

At first it was thought that a patient not responding to ACTH was not likely to respond to another hormone, and in 23 of the 35 ACTH failures no further hormone treatment was attempted. Later it was recognised that this attitude was mistaken, and the remaining 12 were treated by prednisone with success in 8.

Of the 24 who were not treated initially with ACTH, 17 were treated with prednisone with success in 14.

The remainder were given cortisone with success in 3.

In Table IV these figures are set out.

TABLE IV

Treatment	*Initial Success*	*Initial Failure*	*Treatment Subsequent*		*No satis. treatment*
			S	F	
ACTH	61	35	8	4	23
Prednisone	14	3	0	0	3
Cortisone	3	4	0	0	4
	78	42	8	4	
TOTALS ..	86 Success		34 Failure		

It is seen that in 78, or 65 per cent., of cases, initial success was achieved with ACTH according to the criteria already mentioned; and that of 12 failures subsequently treated with prednisone, 8 responded, making a grand total of 71·7 per cent. of success in the 120 cases. The number of successful cases would probably have been higher had the 23 other initial failures on ACTH been subsequently treated with prednisone. In fact, because of the good results with prednisone (and the convenience of its administration) this is now being used initially in place of ACTH.

It thus seems clear that provided infective activity is first subdued with antibiotics, more than 70 per cent. of severe asthmatics with chronic bronchitis will respond very well to hormone treatment.

No patient in this series has been given hormone treatment without prior antibiotic control, as success was thought to be improbable, and the experience with attempted maintenance on hormone without antibiotics, to be referred to shortly, seemed to underline this probability.

In 74 cases, maintenance treatment was given in an attempt to prolong the beneficial effect of the course of treatment in hospital. This was first given as cortisone and later as prednisone, and there seemed little doubt that the latter was the more successful.

A small number (6) quickly relapsed back to their former state, but the great majority maintained their improved health for three months. After this, a considerable and increasing number of patients, month by month, deteriorated, and few maintained any degree of their improvement beyond six months.

There was a slight increase in the total amount of time worked during the twelve months after hospital treatment, and a few patients are still much improved as compared with their previous condition. But the over-all effect upon the general health of the patients in the series was one simply of temporary improvement, though this was usually considerable.

The reasons for the failure of maintenance treatment with hormone have never been widely discussed, though it seems to be the general experience. The failure of a short course of antibiotic treatment alone in these cases is of course much more complete, as few of them show more than moderate temporary improvement.

Now that the present series has shown that a combination of antibiotic and hormone treatment can produce considerable improvement in more than two out of three patients with severe persistent asthma and chronic bronchitis who are not in *status asthmaticus*, nor an acute infective exacerbation, the problem of maintenance becomes more prominent.

Several series of chronic bronchitics on prolonged maintenance treatment with antibiotics have been published and improvement has been claimed, but all agree that this improvement ends with the treatment.

When chronic bronchitis is associated with asthma, it seems reasonable to conclude that failure in maintenance with hormone is due, in most cases, to the persistence of the bronchial infection.

Conclusions

(1) The treatment of patients with severe asthma and chronic bronchitis is perfectly feasible, and success may be expected in two-thirds or more of cases.

(2) The treatment consists of the suppression, first of all, of infective activity by antibiotic therapy, followed by the exhibition of a suitable adrenal hormone in adequate dosage.

(3) Successful initial treatment may be followed by maintenance therapy, but this fails within six months if it consists of hormone alone.

(4) Published series of chronic bronchitics treated by antibiotics on a maintenance basis have shown that considerable improvement occurs as long as the treatment is continued, but not longer.

(5) Successful maintenance treatment of persistent asthma with chronic bronchitis must depend on the use both of antibiotics and hormones on a permanent or semi-permanent basis.

(6) Calculations of the cost of this at the present time make it prohibitive, but it is nevertheless probably medically feasible in most cases.

(7) It is becoming increasingly clear that there is an imperative need to reduce the cost of certain remedies of proved and vital importance, whether by a vast increase in the scale of production, or by other means.

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OBSTRUCTIVE EMPHYSEMA DUE TO CHRONIC INHALED FOREIGN BODY IN THE BRONCHUS

By G. S. Muller Botha

From the Thoracic Surgical Unit, Harefield Hospital, Middlesex

The valve-like action of a foreign body in the bronchus which gives rise to obstructive emphysema was first described by Iglauer in 1911; in 1912 the same author pointed out the radiological features of this condition. This early report was forgotten until the entity was independently rediscovered by Manges, Jackson and Spencer in 1920, and v. Gilse in the same year. At the present time obstructive emphysema in the early stages of inhaled foreign body is well recognised and considered to be extremely common. Jackson and Jackson (1936) stated that obstructive emphysema occurs at some stage in nearly all cases of vegetable foreign body; they found 89 per cent. of 908 cases in which either obstructive emphysema or obstructive atelectasis was present (Jackson and Jackson, 1950). This high incidence is not always found. Out of a total of 35 proven cases of inhaled foreign body which were admitted to Harefield Hospital over the last twelve years, only 5 showed signs of obstructive emphysema. The reasons for this discrepancy are obvious. Obstructive emphysema may be very transient, and develops or disappears over a period ranging from minutes to weeks; radiographs might therefore be taken before it has developed, or after further changes have already occurred. Radiographs might also be taken during the wrong phase of respiration, especially in small children and infants: minor degrees of emphysema are masked when the mediastinum swings over to the invaded side on inspiration, and are easily missed. A high incidence of emphysema is furthermore to be expected when more suspect patients are X-rayed at shorter intervals, especially in a highly specialised unit where all children with X-ray or physical signs of atelectasis or emphysema are labelled "probably non-opaque foreign body; bronchoscopy urgently indicated."

As opposed to acute foreign bodies, obstructive emphysema is extremely rare in cases of long-standing foreign body; in fact, I failed to find any report of such a case in the literature. This is not unexpected as obstructive emphysema depends on a valvular mechanism, and such mechanisms are rapidly made impossible by the granulation tissue reaction which is a normal response to chronic irritation.

The object of this paper is to report a case of obstructive emphysema due to a chronic foreign body in an infant who, according to the history, had bronchial obstruction from birth, and radiological signs of persistent and progressive emphysema of the right lung for three months.

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Case Report

G.S., a male infant of 13 months, born normally as a full-term infant of 6 lb. 10 oz., was admitted to an outside hospital in March 1957 with a chronic cough and wheezing. The mother stated that he developed a persistent cough shortly after birth, which was later associated with a wheeze. These symptoms gradually became worse with periodic exacerbations so that the mother consulted her doctor three months prior to admission, when a diagnosis of bronchitis was made. Cyanosis and choking were absent but further deterioration took place; breathing became more laboured, the cough was more persistent and feeds were taken with reluctance. Vomiting frequently occurred after feeds. A sudden febrile illness brought the patient to hospital.

On admission to another hospital the frail, irritable, under-weight infant had a temperature of 104°, respirations were rapid and inspiratory recession of the intercostal spaces with an expiratory stridor was quite marked. The hæmoglobin was 62 per cent. and the white blood cells were 27,000 c.mm., with neutrophils preponderating at 91 per cent. X-ray of the chest showed increased translucency on the right side and displacement of the mediastinum to the left. Cysts of *Giardia intestinalis* were found in the stool. This responded rapidly to a course of mepacrine and the " bronchitis " improved with antibiotics. The white cell count fell to normal limits, the hæmoglobin rose to 85 per cent. and his general condition improved. Although the expiratory stridor was not affected by ephedrine or prednisolone, it did not appear to distress the patient at all. The emphysema increased. Two months after the patient was first seen he went into status epilepticus which lasted 45 minutes (one previous convulsion just prior to admission).

The infant was admitted to Harefield Hospital in June for bronchoscopy and investigation. The respiratory rate was still rapid with marked expiratory stridor and a loud audible wheeze. Lower intercostal recession on inspiration, especially on the right side, was very pronounced. When the mother was questioned about this she was quite emphatic that the infant had " always " breathed that way and had been as bad for at least six months. The right lung was hyper-resonant and air entry was almost absent. Chest X-ray showed severe obstructive emphysema on the right, mediastinal swing to the left, depression of the disphragm, and widening of the rib spaces (Fig. 1).

Bronchoscopy was carried out under general anæsthesia. A sucking bronchoscope was introduced easily past the cords; the trachea and carina were normal. A small whitish object, at least the size of the bronchial lumen, was lying in the right main bronchus at the level of the orifice to the upper lobe. During inspiration it slipped distally, exposing the upper lobe orifice; on expiration it moved proximally like a little bobbin to occlude the right main bronchus. There was no sign of any granulation tissue, stagnated secretions, pus, ulceration or bleeding. All attempts to remove the obstruction with the biopsy forceps or sucker failed. The appearances were those of a foreign body, but the length of the history, the persistence of obstructive emphysema on the X-rays, the lack of granulation tissue or other signs of chronic inflammation, and the inability to remove the offending party, suggested a benign pedicled neoplasm. For these reasons an attempt at removal through a tracheostomy was not considered; immediate right thoracotomy was performed.

On opening the chest through the bed of the sixth rib the entire lung immediately bulged into the incision. It was pink, extremely soft and papery-thin, lying quite free in the pleural cavity, and had to be squeezed to dispel the air. Once collapsed it only re-aerated gradually despite vigorous inflation by the anæsthetist. The hilum was exposed posteriorly, a transverse slit made in the right main bronchus and a small irregular foreign body was removed with ease from the right main bronchus. No granulation tissue or ulceration was noticed proximal to, distal to or at the site where the body was located, but the bronchus appeared to be excavated where the foreign body was trapped. The bronchus was sutured and the chest closed with drainage.

Re-expansion of the lung was complete on the first post-operative day, but the mediastinum swung to the right, the diaphragm was elevated and the ribs were crowded. There was no sign of collapse and the infant had no symptoms. This radiological appearance was still well marked on discharge, a month after the operation (Fig. 2). Four months after operation the child was well with no physical signs in the chest and a normal X-ray (Fig. 3).

The foreign body consisted of vegetable matter.

Discussion

Different factors (all described in the literature) determine the pathological changes in the lung which follow the inhalation of a foreign body. The size, shape and nature of the body, the site and sojourn, the age of the patient and previous attempts at removal indicate a few of the many variables.

The history in cases of inhaled or ingested foreign body is notoriously unreliable. Nevertheless, it should always be taken carefully and may on occasion be of the greatest value. Although it is virtually impossible that the body in the present case could have caused the " bronchial trouble " which the mother dates from birth, there can be little doubt that it was inhaled quite some time before attending hospital. Persistent obstructive emphysema was radiologically demonstrated from the time of admission at another hospital until operation, a total period of eleven weeks. It is rare even on a single radiological examination to find obstructive emphysema in a case of foreign body of more than two months' duration. Robinson and Mushin (1956) reported one case with emphysema in a patient with foreign body of six weeks' duration who had temporary relief from a previous bronchoscopy after the removal of some nut fragments. It is possible in such a case that the emphysema might be intermittent or that it developed late. Normally, persistent emphysema is never seen: the patient is either bronchoscoped at the first sign of obstructive emphysema and the foreign body removed, or atelectasis supervenes and the radiological appearances change. This was one of the main reasons why the diagnosis of foreign body was questioned, even at bronchoscopy.

The size and shape of the foreign body determine the site of impaction; smooth round ones lodge more peripherally. If a check-valve is formed in the trachea obstructive emphysema of both lungs follows (Manges, 1925); if only a lobar bronchus is obstructed emphysema of that lobe develops (de Haan, 1938). Irregular foreign bodies are more apt to cause obstructive emphysema; smooth ones predispose to earlier atelectasis.

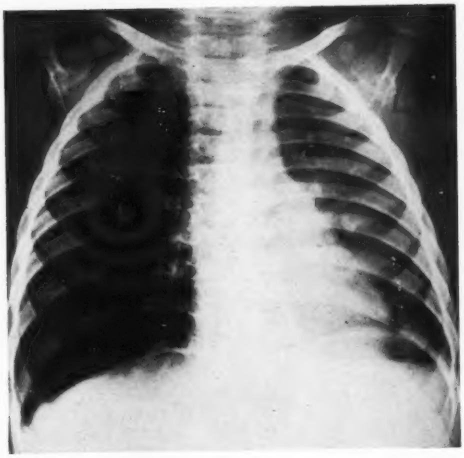

FIG. 1.—Chest radiograph on admission to Harefield Hospital. The typical features of unilateral obstructive emphysema: mediastinal shift, depressed diaphragm and widened rib spaces.

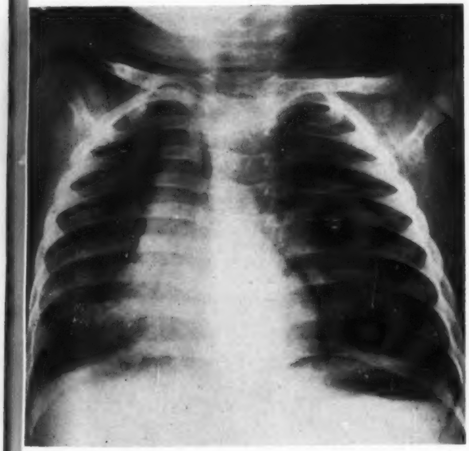

FIG. 2.—Radiograph taken one month after removal of the foreign body. The mediastinum has now moved to the right, the diaphragm is slightly elevated and the ribs are crowded.

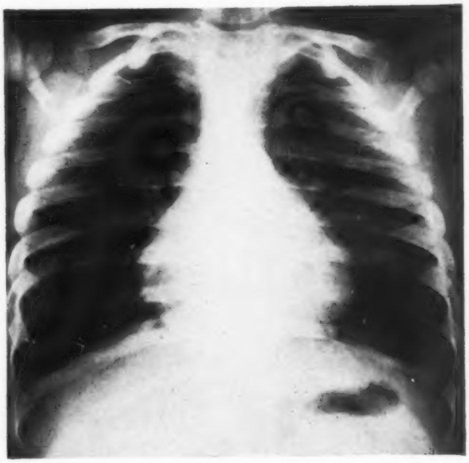

FIG. 3.—Radiograph taken 4 months after operation is normal.

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Hudson and Jarre (1929) confirmed Heinbecker's (1927) experimental observations that the bronchi widen and elongate during inspiration and contract and narrow again on expiration, a fact which might be observed at every bronchoscopy. On inspiration small by-passages open for the ingress of air past the irregular projections of the foreign body; on expiration the bronchus closes and traps the air. The degree of obstructive emphysema entirely depends on the efficiency of this check-valve. It is usually slowly progressive up to a certain stage when the efficiency of the one-way valve fails. The higher pressure then causes a partial leak back so that the degree of emphysema settles at a stationary level. Œdema, when it occurs, enhances the efficiency of the check-valve so that the emphysema is increased to a new stable level, but sooner or later the inflammatory reaction will cause a complete obstruction in both phases of respiration; the distal air will then absorb and atelectasis ensues. This process takes about six days on the average but may take minutes or several weeks. Norris (1948) is of the opinion that the nature and the shape of the foreign body are more important than the time factor in determining whether obstructive emphysema or atelectasis is going to develop. Weinberg (1937) introduced vegetable foreign bodies artificially into the bronchi of rabbits and found obstructive emphysema within the first 20 minutes, infection and collapse in 6 to 24 hours, and frank bronchiectasis in 14 to 58 days. Obstructive emphysema may occur within hours also with metallic foreign bodies (Soulas, 1946).

In some cases the check-valve is more efficient. The tension becomes so great that air dissects outward under the visceral pleura and advances into the mediastinum. Tissue emphysema might even spread into the neck and subcutaneously on the trunk as far as the groins (Maness, 1945; Penta, 1948; Holinger, Andrews and Anison, 1948). It is indeed surprising that this complication was absent in the present case, especially in view of the long duration and the marked obstructive stridor.

One of the most extraordinary features in the present case was the complete lack of granulation tissue as well as other signs of acute or chronic inflammation, which is most unusual because the unsaturated fatty acids in vegetable foreign bodies produce the most rapid and intense acute inflammatory reaction in the bronchi (Patterson, 1919; Pinkerton, 1928; Hara, 1934; Heatley and Clausen, 1930). Weinberg (1938) pointed out, however, that not all vegetable foreign bodies excite such an acute inflammation. Inert substances without irritating soluble fractions may provoke a less severe type of reaction which in some cases is mild and entirely local—the result of mechanical irritation at the site of lodgment. The present case probably falls into this category. The localised excavation in the bronchus prevented the foreign body from being sucked peripherally and collapsing the lower lobe, or being expelled by coughing; a true ball-valve obstruction was thus formed. Inexplicably granulation tissue did not appear. It has been noticed in other cases of foreign body after a sojourn of only eight days, and not one case of chronic foreign body seen at this hospital failed to show signs of granulation. Linton (1957) stressed this finding in his series of long-standing foreign bodies.

It is not often that opportunity presents for studying the outcome of severe chronic obstructive emphysema after the central obstruction has been removed. In cases of short duration the mediastinum centralises immediately, but in the present case the post-operative shift to the right was considerable. This was persistent and more than could be accounted for by technical artefacts. Together with the shift of the mediastinum, the diaphragm rose and the ribs on the right side were crowded. This decrease in size of functioning pulmonary tissue, which lasted more than six weeks, must have been due to decreased vascularity, and interalveolar breakdown and loss of pulmonary elasticity that occurred during the prolonged obstruction. The gradual swingback to normal suggests that the lung tissue has regained its normal architecture and elasticity. One can but speculate on the future of this lung, but the patient will be watched with close interest for signs of bronchial stenosis, bronchiectasis or emphysema.

Differential Diagnosis

It has been said that foreign bodies are unlikely to occur in small infants, and that when they do occur, bronchoscopy provides the answer. During the years 1951-5, 1,262 infants below the age of 1 year died in England and Wales from obstruction or suffocation due to the inhalation or ingestion of food or other objects (Registrar-General's Annual Statistical Review, Tables, Part I, Medical). Although bronchoscopy is usually conclusive, foreign bodies are not always found in cases of obstructive emphysema (Robinson and Mushin, 1956), and this condition might persist even after removal of the foreign body (Gerlings, 1939). In most cases the diagnosis presents no difficulty.

Foreign body must be excluded in every case of obstructive emphysema.

Congenital lobar emphysema, especially in early infancy, has lately aroused considerable surgical interest, and many different factors have been blamed for this condition of which we still know very little. The two best known causes are redundant or infolding bronchial mucosal folds (Nelson, 1932; Royes, 1938; Robertson and James, 1951) and abnormal bronchial cartilages (Overstreet, 1939). In the latter the obstructive valvular mechanism may be due to the absence of cartilage rings in the bronchus (Gross and Lewis, 1945; Ferguson and Neuhauser, 1944); fewer than normal cartilage rings in collapsible walls (Williams, 1952) and chondromalacia of the bronchial tree (Shaw, 1952). Defects of the anterior mediastinum may lead to herniation of one or more lobes with kinking of the bronchi followed by obstructive emphysema (Lewis and Potts, 1951). Fischer, Potts and Holinger (1952) blamed a patent ductus arteriosus for the obstruction. The close association of early lobar emphysema and vascular anomalies, as found by Cottom and Myers (1957), is further evidence that this condition is probably of congenital origin. Aneurysmal veins in the bronchus have been held as a cause (Lewis and Potts, 1951; Robertson and James, 1951). Caffey (1940) stressed the association of infection and viscid secretions in bronchitis with localised obstructive emphysema.

Unilateral or regional obstructive emphysema is not uncommonly found in connection with tuberculous glands (Spivek, 1936) and tuberculous endobronchitis (Eloesser, 1934). Bronchial carcinoma may produce obstructive emphysema to a lobe (Cohen, 1943) or to the entire lung (Morlock, 1934). Benign neoplasms and inflammatory conditions occasionally produce obstructive emphysema (Jackson and Jackson, 1950).

Compensatory emphysema due to atelectasis of a lobe or a lung closely simulate minor degrees of obstructive emphysema. Screening is the most valuable method for differentiating between these conditions. Interstitial, subcutaneous or mediastinal emphysema should always arouse suspicion of an underlying obstructive pulmonary lesion. Minor emphysematous distension of a lobe or a lung may be completely masked by the interstitial air, which also renders any pulmonary lesion less obvious. Tension pneumothorax and large lung or bulbous cysts have also been mistaken for obstructive emphysema.

Abnormal transradiancy of a lobe or of one lung may be confused with obstructive emphysema. Increased radio-translucency is due to the diminution in the size and number of the vascular markings, and may be due to a variety of causes. In agenesis or hypoplasia of a lobe or the entire lung, the pulmonary vessels may be absent or hypoplastic; the right or left pulmonary artery may even be completely absent in otherwise well-developed pulmonary tissue (Emanuel and Pattinson, 1956). Although the affected portion is always more radio-translucent, it is mostly very much reduced in size. Shapiro and Rigler (1948) and Westermark (1938) described radio-translucency in lobes of normal size which followed pulmonary embolism without infarction.

Increased translucency is found in cases of idiopathic " unilateral emphysema " (Dornhorst, Heaf and Semple, 1957) and " abnormal trans-radiancy of one lung " (MacLeod, 1954). Belcher and Pattinson (1957) believe that these cases are examples of hypoplastic lobar arteries. Congenital cystic disease of one lung, especially when it presents with multiple peripheral bronchial dilatations, may show increased radio-translucency (Sellors, 1938).

Summary

Chronic obstructive emphysema due to foreign body in the bronchus is extremely rare. A case is described of a vegetable foreign body in the right main bronchus of an infant of 13 months who had obstructive emphysema that was demonstrable on X-ray for three months. A ball-valve mechanism was found at bronchoscopy and the foreign body was removed by bronchotomy. Granulation tissue was absent. Interesting features are discussed and the causes of obstructive emphysema and transradiancy of part or the whole of the lung are briefly mentioned.

I wish to thank Mr. K. S. Mullard for permission to publish this case and for his helpful criticism.

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THE SPREAD OF LUNG CANCER TO THE BRAIN

BY W. I. B. ONUIGBO

From the Faculty of Medicine, Glasgow University*

THE crux of the problem of cancer dissemination to the brain has long centred on whether this organ has any lymphatic connections. Because this is denied, hæmatogenous metastasis has usually been regarded as indispensable, *e.g.* in lung cancer (Lumsden, 1939; Donaldson, 1947).

Now, it is a striking feature of lung cancer that brain and adrenal metastases frequently co-exist (Barnard, 1943; Boyd, 1953). In a previous paper (Onuigbo, 1957) I demonstrated that the topographical distribution of adrenal deposits accords well with lymph-borne and not artery-borne metastasis. This finding posed the question of whether a similar pattern was demonstrable in the case of brain secondaries. Moreover, it was of interest to find out, as was done in the adrenal study, if any other evidence existed which might indicate that intracranial metastases were conceivably lymph-borne.

This paper, therefore, presents observations which suggest that the spread of lung cancer to the brain is probably by way of lymphatic channels and not necessarily via the arteries. I think that a logical proof of occult lymphatic connections can precede histological or other visible demonstration of their presence. As Rouvière (1938) has said, " the idea of a possible existence of true lymph vessels in the brain substance itself must be entertained."

THEORY OF THE METHOD

A fundamental difference between the topographical distribution of tumour cells by arteries and by lymphatics is utilised.

Arterial Dissemination. Lung cancer hardly attacks the large arteries, but penetrates pulmonary veins and so gains the aorta—a central channel—before arterial embolisation occurs. Consequently, as Willis (1952) implies, and Galluzi and Payne (1955) remark, metastases should be distributed evenly. Thus, unilateral brain metastases cannot be predominantly ipsilateral. Similarly, when bilateral metastases occur, the larger deposits should not predominate in the ipsilateral hemisphere.

Lymphatic Dissemination. Lung cancer commonly involves first the ipsilateral hilar nodes (Thompson, 1952). Next, it usually invades the ipsilateral paratracheal nodes (Allison, 1953). Continuing upwards, it attacks cervical nodes on the same side (Price Thomas, 1948; Gibbon *et al.*, 1955). When lymph nodes are bilaterally implicated, large growths are found mainly on one side (Schuster, 1929). Such larger deposits are generally ipsilateral, for example, in the cervical nodes (Spencer, 1954).

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* Now at the Enugu General Hospital, Nigeria.

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To sum up: for both unilateral and bilateral metastases, if arterial metastasis is the rule, a fifty-fifty distribution of deposits on either side of the brain should materialise; but if lymphatic dissemination predominates, a statistically significant ipsilateral disposition should prevail.

Method of Study

The method is that previously reported for the adrenal metastases of lung cancer (Onuigbo, 1957).

From the necropsy records of the Scottish Medical Schools and the Stobhill General Hospital, Glasgow, bronchial carcinomas were reviewed. In every case showing unilateral metastases in the cerebral or cerebellar hemisphere, it was noted whether the deposits were ipsilateral or contralateral. For bilateral metastases, the side containing the larger deposits was similarly noted. Two hundred and fifty cases fulfilling these criteria were obtained and analysed (see Table I).

Table I.—The Topographical Distribution of Brain Metastases in 250 Cases collected from Scottish Hospitals

City	*Hospital*	*Total*	*I*	*C*	*BI*	*BC*	*I+BI*	*C+BC*
Glasgow	Royal Infirmary (1927–57)	72	29	25	15	3	44	28
	Western Infirmary (1925–57)	51	18	18	9	6	27	24
	Stobhill General Hospital (1949–55)	18	9	4	4	1	13	5
Edinburgh	Royal Infirmary (1923–57)	67	30	15	8	14	38	29
Aberdeen	Royal Infirmary (1938–57)	27	11	9	4	3	15	12
Dundee	Royal Infirmary (1933–57)	15	3	6	3	3	6	9
	Totals	250	100	77	43	30	143	107

I=Ipsilateral; C=Contralateral; BI=Bilateral but ipsilateral deposit larger; BC=Bilateral but contralateral deposit larger.

Table II.—The Topographical Distribution of Brain Metastases in 55 Cases collected from the Literature

Authors	*Total*	*I*	*C*	*BI*	*BC*	*I+BI*	*C+BC*
Davison and Horwitz (1930) . .	4	3	—	—	1	3	1
Ferguson and Rees (1930)	4	3	—	1	—	4	—
Fried and Buckley (1930)	6	—	4	2	—	2	4
Globus (1943)	12	5	3	2	2	7	5
Hall and Harding (1930)	4	1	1	2	—	3	1
King and Ford (1942)	17	8	3	4	2	12	5
Lenshoek (1950)	4	3	1	—	—	3	1
Stern (1954)	4	2	2	—	—	2	2
Totals	55	25	14	11	5	36	19

(Symbols as under Table I)

The available literature was also surveyed by reference to the *Index Medicus* for papers published since 1930 which contained four or more adequately described cases. Fifty-five cases have been collected and analysed (see Table II).

RESULTS

One hundred and seventy-seven cases showed unilateral deposits in the hospital records: 100 being ipsilateral and 77 contralateral. Seventy-three cases showed bilateral growths, of which 43 contained the larger deposits ipsilaterally and 30 did so contralaterally. Thus, in the whole series of 250 cases, ipsilateral tendency was exhibited on 143 occasions, and the contralateral trend was manifest 107 times.

This finding is statistically significant ($\chi^2=5\cdot02$, $p=0\cdot025$), the probability being that an even distribution of metastases as expected from the hæmatogenous theory of metastasis does not occur but, instead, there is an ipsilateral preponderance which is in keeping with lymphatic metastasis.

The 55 cases collected from the literature reveal the same trend ($\chi^2=5\cdot78$, $p<0\cdot025$).

Illustrative Cases

CASE 1. *Left* lung origin. The lymph nodes in relation to the *left* hilum are replaced by neoplastic tissue. In the brain, a very large mass of tumour is situated in the *left* frontal and parietal lobes. Situated in the *left* lobe of the liver is a solitary spheroidal tumour deposit. The *left* adrenal also contains tumour. (*Edinburgh Royal Infirmary* 6/1946.)

CASE 2. *Right* lung origin. The *right* paratracheal lymph nodes are extensively invaded by tumour and form a large mass extending up into the neck above the clavicle; on the left, one of the paratracheal nodes is invaded. Two small tumour nodules are seen, on section, in the *right* frontal lobe; a similar nodule is found in the *right* occipital lobe. On section, numerous secondary deposits of varying size are found scattered throughout the liver, more especially in the *right* lobe. The *right* adrenal is extensively invaded and weighs 130 g. The left is free. (*Aberdeen Royal Infirmary* 92/1952.)

CASE 3. *Right* lung origin. On dissection of the brain, there is a large secondary deposit in the white matter of the *right* parietal cortex. There is also a large secondary in the *right* lobe of the cerebellum which is extending into the *right* side of the pons and medulla. (*Glasgow Western Infirmary A*7285.)

CASE 4. *Left* lung origin. On the under aspect of the *left* cerebellar lobe there is a secondary tumour nodule. There is also a single secondary tumour nodule in the *left* lobe of the liver and another in the *left* adrenal. (*Glasgow Royal Infirmary* 8/1945.)

CASE 5. *Right* lung origin. A secondary tumour the size of a golf ball is found in the *right* frontal region. There is a secondary the size of a pea in the region of the basal nuclei *on that side*. In the left cerebrum there is a secondary the size of a marble. Each adrenal is replaced by a tumour mass, that on the *right* side weighing 120 g. and that on the left 50 g. (*Glasgow Royal Infirmary No.* 15786.)

CORROBORATIVE EVIDENCE FROM THE LITERATURE

(1) The nearer a tumour is to the brain, the more likely it is to spread to this organ, *i.e.* centrifugal spread occurs. Table III, which shows the sources of 1,000 cases of metastatic brain tumours collected from the literature, demonstrates that supradiaphragmatic tumours spread to the brain more often than infradiaphragmatic neoplasms.

TABLE III.—THE RELATIVE INCIDENCE OF METASTASES TO THE BRAIN FROM SUPRADIAPHRAGMATIC TUMOURS (LUNG, BREAST, THYROID, LARYNX, THYMUS, AND ŒSOPHAGUS) AND INFRADIAPHRAGMATIC TUMOURS (STOMACH, SMALL AND LARGE BOWEL, RECTUM, LIVER, PANCREAS, GALL-BLADDER, ADRENAL, AND THE GENITO-URINARY SYSTEM) IN 1,000 CASES

Authors	*Total*	*Supradiaphragmatic tumours*	*Infradiaphragmatic tumours*
Baker (1942)	94	50	44
Baker *et al.* (1951)	85	48	37
Christensen (1949)	54	39	15
Earle (1954)	141	98	43
Earle (1955)	47	32	15
Hare and Schwarz (1948)	84	67	17
Knights (1954)	59	39	20
Lenshoek (1950)	66	54	12
Lesse and Netsky (1954)	158	127	31
Maegher and Eisenhardt (1931) ..	28	24	4
Meyer and Reah (1953)	184	140	44
Totals	1,000	718	282

The lung is considered to be the most frequent source of metastases in the more recent works (Boyd, 1925; Evarts Graham, 1936; Biggart, 1949; Russell Brain, 1955). The breast is so regarded by Willis (1953) and the earlier authorities (Mott, 1901; Harvey Cushing, 1910; Waring, 1928). Perhaps, on balance, the lung comes first in men and the breast in women (Knights, 1954; Earle, 1955).

It is noteworthy that, after the lung and breast, some list the thyroid next (Hughes, 1952; Nettleship, 1952; Earle, 1955) and others put it high in their list (Miller and Davidson, 1938; Bucy, 1943; Lenshoek, 1950).

No theory of blood flow succeeds in explaining the above findings. If portal venous blood flow through the liver before reaching the lungs is an important factor, then extraportal tumours like those of the breast and uterus should have a comparable incidence, other things being equal.

(2) Another anomalous finding which is also explicable on the basis of centrifugal lymphogenous dissemination is the peculiar position occupied by

the cerebellum in intracranial metastasis. Thus, Dorothy Russell (1950) affirmed that "considering its relatively small size the cerebellum must be regarded as a site of predilection." Lenshoek (1950), a Dutch neuro-surgeon, said, "The relatively frequent occurrence in the cerebellum is remarkable." Again, according to Meyer and Reah (1953), "there is a predilection for the cerebellum which remains unexplained."

Anatomically, Reid's (1848) figures and Jamieson's (1950) assessment show that the cerebellum, or little brain, is only about one-eighth of the size of the cerebrum. Yet, pathologically, it suffers metastasis half as often. This is evident in Table IV in which I have analysed 500 published cases.

TABLE IV.—THE RELATIVE FREQUENCY OF CEREBELLAR AND CEREBRAL METASTASES IN 500 CASES

Authors	*Total*	*Cerebellum*	*Cerebrum*
Baker (1942)	92	27	65
Earle (1954)	207	75	132
Hare and Schwarz (1939)	42	16	26
Lesse and Netsky (1954)	87	36	51
Tom (1946)	72	23	49
Totals	500	177	323

531

Even if deposits in the cerebellum and cerebrum are enumerated, the same picture is obtained. For example, Baker *et al.* (1951) reported that, in 70 cases in which multiple nodules were counted, 44 lesions were found in the cerebellum and 92 in the cerebrum.

Suitability of "soil" can hardly explain cerebellar susceptibility in metastasis to central nervous tissue. Clearly, the quantity of arterial blood does not account for it. In consequence, the probability of lymphogenous invasion, which makes cerebellar selection intelligible, ought to be entertained.

A further point of analogy exists. When cancer spreads to lymph nodes, nearby nodes tend to contain larger deposits although, on occasion, they may be "skipped" and distant ones are preferentially attacked (Kolodny, 1925; Herbut, 1955). It is of interest, therefore, that the occipital lobe, which is suprajacent to the cerebellum, is the lobe less likely to be metastasised (Kinnier Wilson, 1940; Störtebecker, 1954), or less likely to contain large deposits (Dickson and Worster-Drought, 1936), or solitary deposits (Stern, 1954). The occipital lobe would seem to be sheltered in this way, although the cerebellum may be skipped and this lobe involved.

(3) Macroscopic brain metastases are often solitary. Since they occur in over one-third of cases, Stern (1954) said, "It is difficult to accept the finding as one of pure chance." Her figures and those of Davison and Horwitz (1930), Flavell (1949), Meyer and Reah (1953) and Halpert *et al.* (1954) show that 84 cases had solitary and 157 had multiple deposits.

Yet, carcinomas of the bronchi are the best located to scatter tumour to the brain (Byrom Bramwell, 1888; Anderson, 1952). Indeed, Holmes Sellors (1954) was satisfied, as was Hill (1931), that in lung cancer " distant metastasis is less common than might be expected." Lymphogenous and not arterial spread satisfactorily explains limited metastasis. Davison and Horwitz (1930) did suggest that solitary brain deposits with cervical node invasion argued for lymphatic metastasis. Notably, their second case, a *left* lung growth, showed a single mass in the *left* cerebral hemisphere and other deposits in the *left* adrenal, *left* kidney and pancreas.

(4) The outstanding histopathological features of brain metastases include the common finding of tumour cells in perivascular spaces (Hassin, 1933), and the difficulty of demonstrating them inside vessels (Globus and Meltzer, 1942). The latter authors note that intracerebral spread occurs mainly via perivascular spaces. Tumour cells surround even capillaries (Cappell, 1951). At times macroscopic appearances are deceptive and only microscopy reveals the true state of affairs (Fischer-Williams *et al.*, 1955).

Two controversial questions are asked. First, do lymphatics effect connections with these perivascular spaces? Many anatomists, and His (1867) was among them, thought so. Recently, Lups and Haan (1954) took this view. Secondly, are the subarachnoid spaces and the lymphatic system connected? Brierley and Field (1948) reviewed the matter and found that Indian ink introduced into the cranial subarachnoid appeared within four hours in cervical nodes and ultimately in intrathoracic nodes. Long ago, Hassin (1919) concluded that Nature herself carried out this experiment retrogradely.

Conclusion

In conclusion, the indications would seem to be that the mode of spread of cancer, not only to *lymph nodes* but also to the *various organs* like the brain and adrenal, is the same, namely lymphogenous—at least in the main. Such a unitary concept of metastasis is of fundamental importance and deserves concerted scrutiny. As Lord Rutherford—see Sampson Handley (1955)—has said, " Nature appears to work in a simple way, and . . . the more fundamental the problem the simpler are the conceptions needed for its explanation."

Summary

The existence of a lymphatic drainage for the brain is disputed. In consequence, the current view is that lung cancer metastasises to this organ via the arteries.

Theoretically, arterial scattering of tumour emboli should result in an even distribution of deposits on either side of the brain. Similarly, lymphogenous dissemination to the brain would lead to ipsilateral preponderance of deposits.

Two hundred and fifty cases of brain metastases following lung cancer are analysed. The cases in the series are those in which metastases occurred either wholly or mainly in one cerebral or cerebellar hemisphere.

It is found that the metastatic trend is ipsilateral rather than even. A statistically significant result was obtained, for there were 143 growths which were wholly or mainly ipsilateral as against 107 contralateral ones.

Fifty-five cases collected from the literature also exhibited a statistically significant ipsilateral preponderance. Five cases illustrative of this trend in metastasis are appended.

Corroborative evidence is adduced from the literature:

1. Supradiaphragmatic tumours metastasise to the brain more often than infradiaphragmatic growths.
2. The relatively nearer cerebellum is a site of metastatic predilection.
3. Multiple macroscopic metastases occur only twice as often as the solitary.
4. The histopathology of metastatic brain tumours points to the importance of perivascular and subarachnoid spaces.

It is concluded that a unitary theory of metastasis to both the lymph nodes and organs like the brain and adrenal is possible and may be of fundamental importance.

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LUNG ABSCESS FOLLOWING ASEPTIC PULMONARY EMBOLISM

By K. Davison

From Newcastle General Hospital

Pulmonary embolism is regarded as an ætiological factor in only a small proportion of cases of lung abscess—3·9 per cent. in one large series (Hedblom, 1944)—and usually the emboli are infected initially (Hussey, 1950). However, the possibility of a lung abscess developing after aseptic pulmonary embolism is recognised (Welch, 1920) and a number of cases are reported in the literature (Levin *et al.*, 1948, 23 cases; Chester and Krause, 1942, 17 cases; Coke and Dundee, 1955, 5 cases; Murray and Mackenzie, 1942, 2 cases; Hollman, 1935, Gsell, 1935, Shirley Smith, 1938, Short, 1951, and Ring and Bakke, 1955, 1 case each). Empyema following such an abscess is also reported (Steinberg *et al.*, 1937, 4 cases; Touroff, 1933, 1 case).

Cavitation of a pulmonary infarct without abscess formation was observed in 5 out of 100 consecutive cases by Soucheray and O'Loughlin (1953), who thought that antibiotics had prevented secondary infection. Short (1951), who found only one lung abscess in 120 cases of pulmonary infarction, also attributed its infrequency to the use of antibiotics. Before the antibiotic era opinion ranged from that of Castleman (1940), who considered that superimposed infection of a pulmonary infarct was a rare coincidence, to that of Gsell (1935), who thought that infarction with secondary infection was a common cause of lung abscess which was often missed. The incidence of lung abscess in cases of pulmonary infarction at necropsy is variously recorded as 17 cases in 344 or 4·9 per cent. (Chester and Krause, 1942), 2 cases in 349 or 0·6 per cent. (Murray and Mackenzie, 1942), and 23 cases in 550 or 4·2 per cent. (Levin *et al.*, 1948); in this last series it occurred in 0·36 per cent. of all necropsies. Coke and Dundee (1955) found that in a number of post-mortem studies of pulmonary infarction published since 1930 the overall incidence of abscess formation was 2·7 per cent., of which less than half were diagnosed before death.

In view of the apparent infrequency of this condition it is considered worth reporting the following 3 cases, in each of which a lung abscess developed after aseptic pulmonary embolism.

Case Reports

Case 1. A 68-year-old man had a typical pulmonary embolism, with chest pain, dyspnœa and hæmoptysis, two days after admission to a surgical ward for investigation of hæmaturia. Crepitations were heard at the left lung base,

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but a chest X-ray showed normal lung fields. There was no evident peripheral venous thrombosis, though the left leg had been swollen three weeks previously; an electro-cardiogram showed S.1 and inverted T.2 and T.3 (Fig. 4). Anticoagulants were not given because of the hæmaturia, but he improved rapidly and was able, five days later, to undergo endoscopic prostate resection with diathermy to bladder papillomata, under general anæsthesia. He remained well till the sixth post-operative day, when he had a further sudden episode of dyspnœa and right-sided chest pain but without hæmoptysis. Chest and legs were clinically normal, temperature 98·4° F., W.B.C. 10,200 per cu. mm. (polymorphs 80 per cent., lymphocytes 17 per cent., monocytes 3 per cent.), and the chest X-ray remained unaltered, but an electrocardiogram now showed a partial right bundle branch block (Fig. 4). It was evident that another pulmonary embolism had occurred and, as hæmaturia had ceased, anticoagulant therapy was commenced. Progress was uneventful for the next eight days when his temperature, which had been normal, rose to 101·6° F., W.B.C. 22,350 per cu. mm. (polymorphs 78 per cent., lymphocytes 10 per cent., monocytes 2 per cent.). Soluble penicillin, 500,000 units six-hourly intramuscularly, was commenced but, although he was not particularly ill, intermittent pyrexia continued and seven days later a chest X-ray demonstrated a triangular opacity with several small cavities in the right upper lobe (Fig. 1A). Purulent sputum was now produced and, as culture yielded a pure growth of pathogenic staphylococci sensitive only to erythromycin, this antibiotic was substituted for penicillin in an oral dose of 0·5 g. six-hourly. Ten days later the X-ray showed a multilocular cavity (Fig. 1B) which after a further seven days had become a single cavity with a fluid level (Fig. 1C). There was now no pyrexia, W.B.C. 8,500 per cu. mm., and fourteen days later the cavity had almost disappeared and the electrocardiogram was almost normal. He was discharged fifty-five days after his second pulmonary embolism and has remained symptom-free. A subsequent chest X-ray showed only slight scarring at the site of the abscess.

Case 2. A 78-year-old woman was admitted with clinical and radiological signs of an infarct of the left lower lobe associated with thrombophlebitis of varicose veins in her right leg; an electrocardiogram showed a right bundle branch block. After treatment with anticoagulants and penicillin she was discharged thirty-eight days later, when her chest was clear and the thrombophlebitis had subsided.

She was readmitted fifteen days later with thrombophlebitis of varicose veins in the left leg, further infarction of the left lower lobe and mild diffuse bronchitis; temperature 97·8° F., W.B.C. 11,350 per cu. mm. (polymorphs 70 per cent., lymphocytes 26 per cent., monocytes 4 per cent.). Anticoagulant therapy and procaine penicillin 300,000 units b.d. intramuscularly were commenced, but four days later there was another pulmonary embolic episode with dyspnœa and right-sided chest pain. She improved and was apyrexial for the next fourteen days, but then she developed a swinging temperature of up to 102° F., and produced purulent sputum; W.B.C. 20,800 per cu. mm. (polymorphs 78 per cent., lymphocytes 15 per cent., monocytes 5 per cent., eosinophils 2 per cent.). Chest X-ray demonstrated an opacity in the right upper lobe with early cavitation. Sputum culture yielded penicillin-resistant staphylococci, so oral aureomycin 0·5 g. six-hourly was given and postural drainage was instituted. The pyrexia subsided within two days, but heart failure began to develop and a chest X-ray then showed a fluid level in the right apical cavity, cardiac enlargement and pulmonary congestion (Fig. 2). Three weeks later the cavity had almost disappeared, but heart failure increased, and the patient died seventy-two days after re-admission. Permission for autopsy was not obtained.

CASE 3. A 41-year-old housewife, with bilateral varicose veins, developed an acute spontaneous thrombophlebitis in the right leg. She remained in bed at home, but on the eighth day suddenly developed dyspnœa and right-sided pleuritic pain and was admitted to hospital. Though cyanosed and breathless, her chest was clinically clear, but the right long saphenous vein was thrombosed and inflamed. Pulmonary embolism was diagnosed and treatment commenced with morphine, oxygen and anticoagulants. Chest X-ray next day showed normal lung fields, but an electrocardiogram showed Q.2 and 3, and inverted T waves in leads 2 and 3 and all the chest leads (Fig. 5); temperature 98°F., W.B.C. 7,500 per cu. mm. Her course was satisfactory and without pyrexia for the next seven days, but a further episode of dyspnœa with transient pleural friction at the left lung base then occurred. Four days later her temperature began to rise and reached 103° F. after a further three days; W.B.C. 13,000 per cu. mm. (polymorphs 85 per cent., lymphocytes 12 per cent., monocytes 2 per cent., eosinophils 1 per cent.). Clinical examination was negative, but a chest X-ray demonstrated consolidation of the apical and axillary segments of the right upper lobe with a cavity in the apical segment (Fig. 3A). Crystalline penicillin 500,000 units, six-hourly intramuscularly, was given but, as the pyrexia was unaffected, was replaced three days later by oral aureomycin 0·5 g. six-hourly. The pyrexia subsided but reappeared five days later and assumed a swinging character, reaching 102° F., and purulent sputum was produced. The pyrexia persisted until aureomycin was replaced by erythromycin in the same dose, though the predominant organism in the sputum was a pathogenic staphyloccus sensitive *in vitro* to the common antibiotics. The cavity became smaller, the electrocardiogram returned to normal, except for persistent Q.2 and Q.3 (Fig. 5), and, as the patient was ambulant and the thrombophlebitis quiescent, anticoagulants were stopped on the thirty-sixth day. Eight days later, however, there was another severe pulmonary embolism, E.C.G. changes reappeared (Fig. 5) and a chest X-ray demonstrated a fresh opacity in the right lower lobe with elevation of the diaphragm (Fig. 3B). The right long saphenous vein was still thrombosed but no longer inflamed. Anticoagulants were recommenced and there was gradual improvement. Sixty days after admission her inferior vena cava was ligated and recovery was satisfactory. A chest X-ray two months later showed only scarring at the right apex.

Discussion

In these three patients thrombosed leg veins were the source of repeated pulmonary emboli. The absence of clinical signs in the legs of case 1 is compatible with the presence of phlebothrombosis (Allen *et al.*, 1955), especially as the leg had been swollen three weeks previously. Radiologically clear lung fields, as in cases 1 and 3, are consistent with serious and repeated pulmonary embolism (Homans, 1943), and in some cases radiological signs may appear only when secondary infection occurs (Sante, 1930).

The question arises whether or not these emboli were initially infected. The lesion in case 1 is typical of so-called phlebothrombosis in which primary inflammation of the vein is absent, whereas cases 2 and 3 are examples of thrombophlebitis in which inflammatory changes in the wall of the vein are said to initiate thrombosis (Ochsner and Debakey, 1939). This concept of the ætiology of venous thrombosis has been criticised on the grounds that phlebitis can develop as a reaction to the thrombus (Allen *et al.*, 1955), and moreover, in cases of spontaneous thrombophlebitis of varicose veins without skin sepsis or ulceration, cultures from excised lesions have been sterile (Allen *et al.*, 1955; Edwards, 1937). The development of a single abscess in each case, despite repeated pulmonary embolism and the interval of eight to fourteen days between the embolic episodes and the appearances of signs of infection, suggests that infection occurred secondarily. These features conform to those of other reported cases (Levin *et al.*, 1948; Chester and Krause, 1942) and are in contradistinction to septic pulmonary embolism in which lung abscesses are multiple and there is usually an obvious focus of infection with high temperature and leucocytosis preceding the occurrence of embolism (Hussey, 1950; Hussey and Katz, 1945).

In the absence of a bloodstream infection bacteria must have reached the infarcted area of lung *via* the bronchial tree. Experiments with dogs have shown that lung abscess is a rare occurrence after pulmonary embolism unless accompanied by the intra-bronchial insufflation of infected material (Van Allen *et al.*, 1929). Infected material can be aspirated from the mouth and nasopharynx to all parts of the lung during sleep, or if the cough reflex is suppressed and necropsy evidence of adjacent atelectasis and bronchitis is frequent in these cases (Levin *et al.*, 1948). The larger infarcts are more liable to abscess formation (Levin *et al.*, 1948), and this is probably due to a relative inadequacy of the collateral bronchial circulation, which, after pulmonary embolism, is usually sufficiently increased to prevent necrosis (Mathes *et al.*, 1932).

None of these 3 cases had dental or nasopharyngeal sepsis, though morphine, a potent cough suppressant, was given at first to cases 1 and 3. Case 2 had a diffuse bronchitis and case 1 may have had a low-grade bronchitis following inhalation anæsthesia. However, staphylococcal lung abscess, of which these cases are examples, does not usually occur in association with bronchial embolism, but is often secondary to co-existing or pre-existing disease of the lung (Brock, 1952). The development of these abscesses shortly after pulmonary vascular embolism is unlikely to be coincidental. It is suggested that the vascular emboli rendered the affected segments of lung less able to withstand infection by inhaled staphylococci.

It is possible that antibiotic therapy from the beginning would have prevented these abscesses, but, at the time, in the absence of clinical and radiological chest signs and evidence of infection, it did not seem to be

PLATE XIX

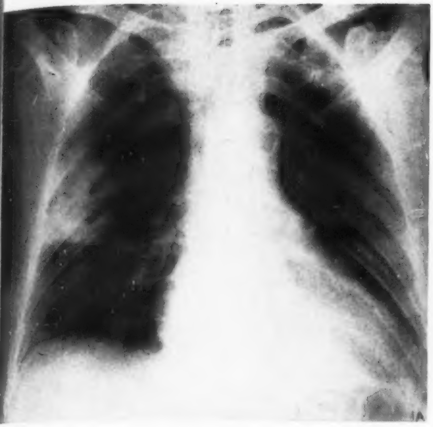

FIG. 1A.—Case 1. 15 days after pulmonary embolism. Triangular opacity with several small cavities in the right upper lobe.

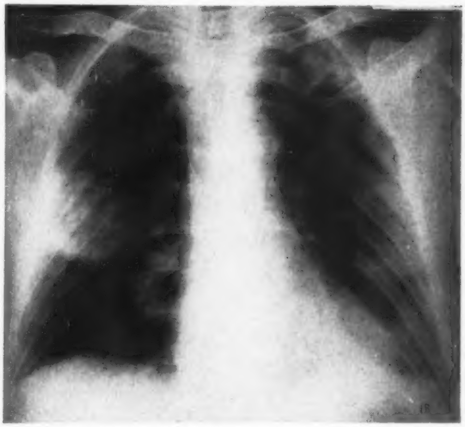

FIG. 1B.—Case 1. 10 days later. Cavities coalescing.

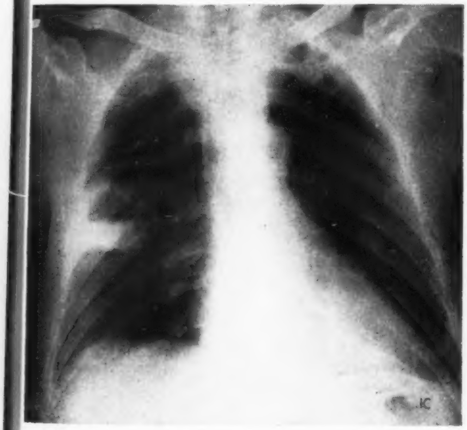

FIG. 1C.—Case 1. 6 days later. A single cavity with a fluid level is now present.

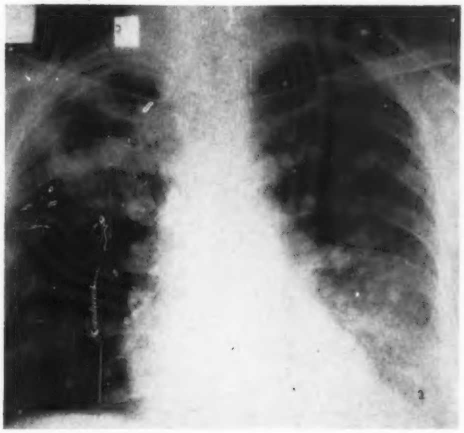

FIG. 2.—Case 2. 37 days after admission. There is cardiac enlargement, generalised pulmonary congestion, opacity in the left lower lobe, and consolidation in the right upper lobe with a cavity containing a fluid level.

PLATE XX

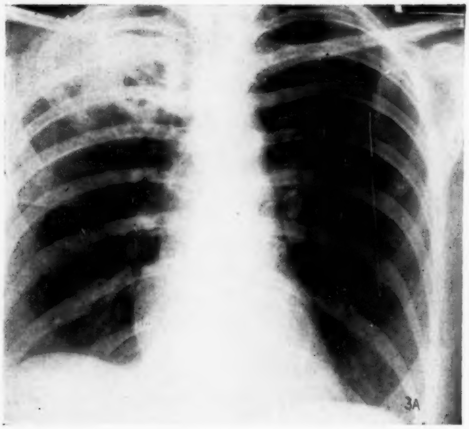

FIG. 3A.—Case 3. 16 days after admission. Opacity in the right upper lobe with cavity formation.

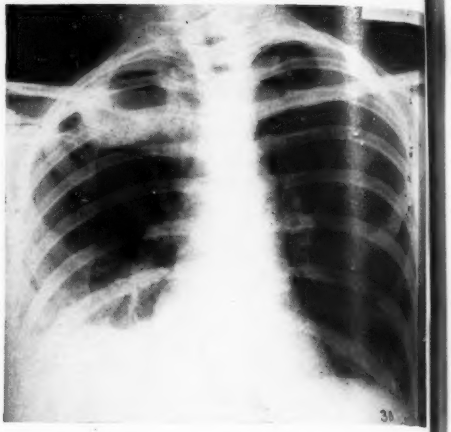

FIG. 3B.—Case 3. 4 weeks later. Cavity at the right apex with fresh pulmonary infarction in the right lower lobe.

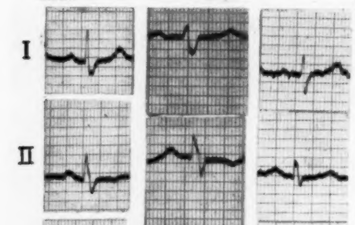

FIG. 4

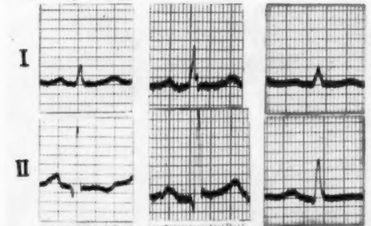

FIG. 5

FIG. 4 — E. C. G. Case 1.

(*a*) After first pulmonary embolism showing prominent S-waves in leads 1, 2 and V.7 with T-wave inversion in 1 and 3.

(*b*) After second pulmonary embolism. Partial right bundle branch block now present.

(*c*) 45 days later. E.C.G. normal. T-wave in lead 2 now upright.

FIG. 5 — E.C.G. Case 3.

(*a*) After initial pulmonary embolism. Prominent Q in leads 2 and 3, inverted T-waves in leads 2 and 3 and chest leads.

(*b*) 36 days later. T-waves now upright.

(*c*) After further pulmonary embolism on 44th day. T-waves again flattened or inverted.

indicated in cases 1 and 3. Procaine penicillin in average doses did not prevent the abscess developing in case 2 and, in view of the resistant organisms isolated from the sputum, it is unlikely that penicillin would have been effective in cases 1 and 3.

Chester and Krause (1942) found that the lung abscess was often the presenting feature, obscuring the underlying infarct which was only disclosed at necropsy. It is certainly worth reiterating their comment that aseptic pulmonary embolism should be considered as a possible factor in every case of lung abscess, especially in conditions, such as heart failure or following operations, where pulmonary embolism is more liable to occur.

Summary

Three cases are reported in which a single lung abscess developed following repeated pulmonary embolism. Reasons are given for regarding the emboli as initially aseptic, staphylococcal infection occurring secondarily *via* the bronchi. The literature is briefly reviewed and the suggestion made that aseptic pulmonary embolism should be considered as a possible ætiological factor in cases of lung abscess.

I am grateful to Dr. W. G. A. Swan, Dr. F. S. Jackson, Mr. J. Swinney and Mr. J. D. Rose for permission to report these cases.

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INTRATHORACIC GOITRE

By N. S. Dontas

From The London Chest Hospital

Intrathoracic extension of the thyroid gland is rare. Wakeley and Mulvany (1940) found 20 cases amongst 1,265 thyroidectomies with partial intrathoracic goitre, but in only 3 of these was the thyroid gland in the neck apparently normal. Crile in 1939 had 97 intrathoracic goitres out of 11,800 thyroidectomies. At the Lahey Clinic, out of 28,000 patients who have been operated on for goitre only 100 had an extension within the chest. In 3 of them preoperative diagnosis was doubtful and the tumour was removed through a thoracotomy incision. More recently Lange (1953) collected 1,000 thyroidectomies from the New End Hospital in London and found retrosternal extensions in 23·5 per cent. of all cases.

During the past ten years, 51 patients with intrathoracic goitre have been treated at the London Chest Hospital. In all these cases either the greatest diameter of the thyroid gland was below the thoracic inlet, or the entire goitre was within the mediastinum. An intrathoracic goitre arises either from the isthmus or from either lower pole of the thyroid gland. It descends downwards into the mediastinum between the pretracheal and prevertebral fascia according to the resistance of the cervical muscles anteriorly and the trachea and vertebræ posteriorly. Apart from the position of the infra-hyoid muscles, the influence of the swallowing mechanism predisposes the thyroid gland to descend and subsequently to grow into the mediastinum. The connection between the thyroid gland in the neck and the intrathoracic goitre then diminishes and often leaves only a very small band of tissue which is provided with a blood supply from the inferior thyroid artery. Occasionally the arterial blood for the intrathoracic goitre comes from the subclavian artery or even from the aorta.

ANATOMY

Intrathoracic goitres usually lie in the anterior mediastinum behind the sternum and in front of the trachea, great vessels and recurrent nerves. Only rarely does an intrathoracic goitre grow in the posterior mediastinum and then it extends behind the inferior thyroid artery, the carotid sheath, the innominate and subclavian arteries and the innominate veins. Goitre in the posterior mediastinum is a very rare condition and only 25 cases have hitherto been described. The largest number of cases reported by one author was 6, collected by Sweet (1949). There were 9 patients with goitres of the posterior mediastinum in the present series.

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PATHOLOGY

The pathology of an intrathoracic goitre is usually of the nodular type with a sharp and well-defined capsule. Only in a small percentage are there cystic changes, but hæmorrhagic degeneration and calcification are found in considerable number. Only in four cases in this series was malignancy present, but it is uncertain whether or not the original lesion was a benign tumour of the thyroid gland.

SIGNS AND SYMPTOMS

The main symptoms of an intrathoracic goitre are due to deviation or compression of the vital organs lying in the thoracic inlet or the upper mediastinum. In most cases the thyroid tumour lies in the anterior mediastinum, displacing the trachea either backwards or sideways. The latter deviation is more common. In this series 23 cases of intrathoracic goitre were growing from the left lower pole and displacing the trachea to the right, and 17 were arising from the right lower pole and producing deviation to the left. In 2 patients who suffered from severe distress the intrathoracic goitre was pressing the trachea backwards, causing its partial collapse. In 4 cases when the tumour surrounded the trachea the compression was bilateral. Five patients with posterior mediastinal goitres showed severe forward displacement of the trachea. Compression or deviation of the trachea caused a variable amount of respiratory distress in 25 patients. Nine presented with severe orthopnœa, but in 17 cases, in spite of moderate deviation of the trachea, no dyspnœa was apparent.

Compression of the trachea reduces the diameter of its lumen and gives rise to stridor, as well as to a diminution of air intake, and as a result increased respiratory disturbance and cyanosis may occur. The accumulation of viscous bronchial secretions in the area of the stenosed trachea can produce almost complete obstruction and attacks of suffocation are evident. Infiltration of the wall of the trachea is always apparent in cases of malignancy at a late stage, and it was present in 3 of the 4 malignant intrathoracic goitres in this series.

Pressure symptoms of the intrathoracic goitre upon the great vessels are not uncommon. Slight enlargement of the thyroid gland produces compression of the internal jugular veins, causing dilatation of the superficial thoracic veins. A further enlargement may cause partial obstruction of the right or left innominate veins or even compression of the superior vena cava. As a result of this, apart from the engorgement of the neck and arms, œdema of the face, persistent headaches and even cyanosis appear in a short time. Partial vena caval obstruction was present in 8 cases and in 3 of them symptoms had been noticed for over two months.

Cough is an unusual symptom; nevertheless it has a distinctive character. The typical stridor on inspiration is followed by a whistling through the narrowed lumen of the trachea. Cough has been evident in 10 cases, but only in 5 was it productive. Hæmoptysis was the predominant symptom of the 4 malignant goitres, and in 3 of them this was due to the malignant infiltration of the wall of the trachea. Pain is practically an unknown symptom, even in cases of malignancy, and this is the reason why patients are admitted to hospitals at a late stage. Moreover, a feeling of fullness in the neck and the upper mediastinum is a common and frequent symptom. Displacement of the œsophagus usually follows the deviation of the trachea. In a few cases, especially those lying in the posterior mediastinum, where the œsophagus was displaced forwards dysphagia ensued. This was present in 5 cases.

Involvement of a recurrent laryngeal nerve, producing paralysis of a vocal cord, does not mean that a malignant tumour of the mediastinum is present, or that it is caused by a malignant intrathoracic goitre. In this series, 3 out of 4 patients with malignant goitres had a paralysed cord, but the same complication was present in 5 more cases suffering from a simple adenomatous goitre. Another symptom, frequently found in cases of intrathoracic goitre, is a choking feeling on bending forwards, which produces considerable pressure of the trachea. In a so-called " plongeant goitre " whose diameter is small and not adherent, this pressure is more marked when, on coughing, it passes in and out of the thoracic inlet without difficulty. Frequent attacks of " bronchitis " are a common sequel to intrathoracic goitre, present in 16 cases.

Intrathoracic goitres seldom present symptoms of thyrotoxicosis, although a mild degree of activity of the thyroid gland might be detected. Only 4 cases in this series showed palpitations, tachycardia and tremor. Obvious enlargement of the thyroid gland in the neck is not always present with intrathoracic goitre, although it has been detected in all cases which have finger-like projections in the mediastinum. The presence of a goitre in the neck was noticeable in 27 cases and in 10 more the upper pole of the thyroid gland could be felt at the episternal notch. In all these the retrosternal extension was enormous.

INVESTIGATIONS

The diagnosis of an intrathoracic goitre is based on clinical and radiological evidence, though differential diagnosis can be difficult. A palpable cervical enlargement of the thyroid gland with an abnormal shadow in the upper mediastinum justifies the belief that there is a retrosternal extension. In such a case palpation of the inferior pole of the thyroid gland may suggest that the retrosternal tumour is detached, but has a very narrow attachment. Palpation of the upper pole of an intrathoracic goitre is possible during expiration at the episternal notch.

The plain postero-anterior X-ray shows a shadow in the upper mediastinum with deviation of the trachea to one side, and in some cases,where compression of the trachea is marked, a penetrating X-ray will show the degree of stenosis. The lateral view is helpful to identify the position and extension of the shadow into the mediastinum in relation to the trachea and great vessels. In 15 cases the lower border of the intrathoracic goitre was well below the arch of the aorta. Tomograms may be of assistance in demonstrating the site and

PLATE XXI

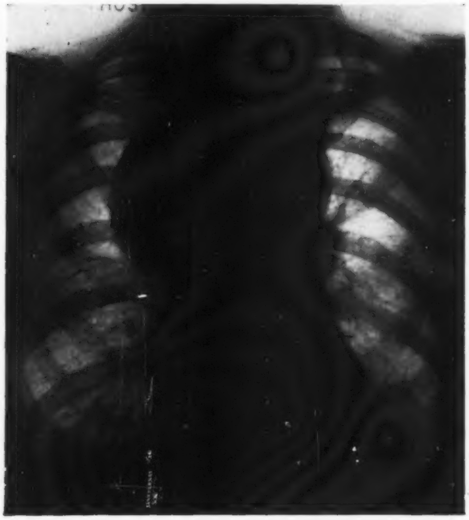

FIG. 1.—W.A., age 61, female. Previous thyroidectomy 1919. Enormous intrathoracic goitre of the anterior mediastinum. It was removed through a combined collar incision with split of the sternum.

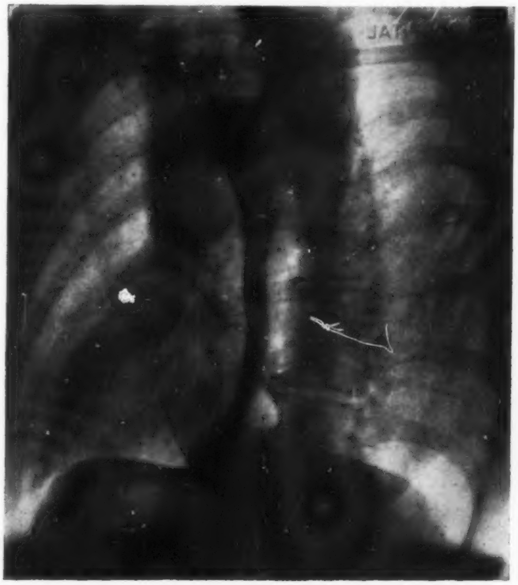

FIG. 2.—Same patient with Fig. 1. Barium swallow demonstrates the oesophagus being compressed and deviated.

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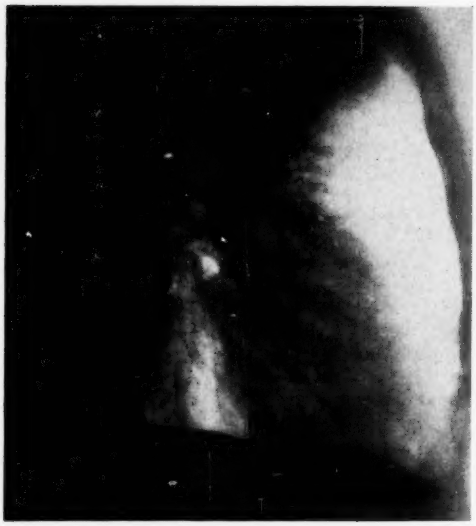

FIG. 3.—J.L., aged 51, male. Enlarged intrathoracic goitre of the posterior mediastinum arising from the left lower pole and displacing the trachea forwards.

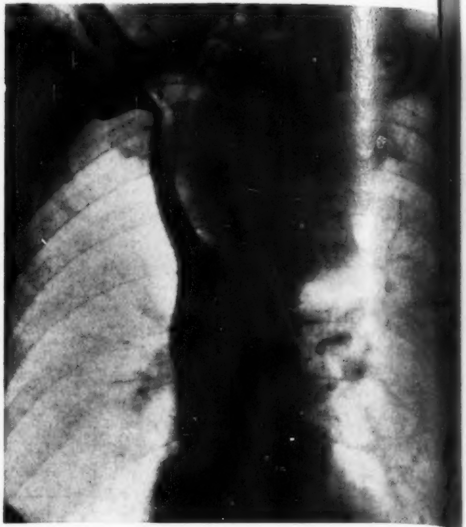

FIG. 4.—Same patient as fig. 3. Angiocardiograph shows partial filling of a dilated collateral vein joinin the subclavian vein. The right innominate vein narrowed transversely and displaced to the right by intrathoracic goitre.

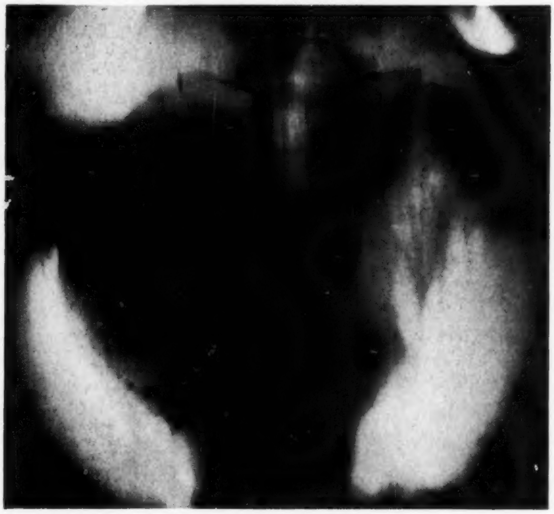

FIG. 5.—A.P., age 57, male. Tomogram cut 11 cm., shows extremely enlarged intrathoracic goitre with a very marked deviation and compression of the trachea to the left at the level of the arch of the aorta.

size of the tumour. A barium swallow is contributory, showing the presence of any compression or deviation of the course of the œsophagus and even more to differentiate any actual abnormality. Only in 5 cases was a small indentation of the œsophagus apparent, producing symptoms of dysphagia (Figs. 1-5).

Angiocardiography is helpful mainly in cases of clinical evidence of obstruction to demonstrate a delay of the contrast media passing through the venous system, or an improper filling or even a complete obstruction of one part of the circulation. In this series it has been possible to show in 4 patients a partial compression of the innominate vein and the superior vena cava. Laryngoscopy is necessary to confirm the condition of the vocal cords. Bronchoscopy must be undertaken when the predominant symptom is hæmoptysis to exclude an obvious infiltration of the tracheal wall. In such cases major complications may arise, as the deviated and compressed trachea is very easily damaged. On fluoroscopy movements of the intrathoracic goitre with swallowing can be seen, as well as the existence of pulsation of the tumour under diagnosis. On the other hand, it is not always possible to be certain if the pulsation of a mediastinal tumour is expansile or transmitted.

The determination of a mediastinal tumour as intrathoracic goitre might be helpful with the administration of a tracer dose of radioactive iodine (^{131}I). A Geiger counter can define the uptake and distribution of iodine by the thyroid, and establish the function of the gland. Nevertheless in nodular goitre the distribution of ^{131}I is unequal and in carcinoma of the thyroid the uptake is very small, so that the intrathoracic portion might be misjudged. The value of this investigation is considerable when the result is positive, but it must not alter our decision when the result is negative.

Treatment

Intrathoracic goitres vary enormously in size and position, so that a careful pre-operative study is necessary to decide on the best method of surgical treatment. The degree of specific symptoms depends on the pressure on the vital organs. Consequently a small goitre, wedged and growing in the thoracic inlet between the sternum and the trachea, will produce far more acute symptoms of dyspnœa and suffocation by comparison with an enormous tumour lying a few inches below that point, such as in the mediastinum. This was seen in 2 cases in this series, and after the resection the diameter of the intrathoracic goitre measured 1 inch.

The majority of the intrathoracic goitres are lying in the anterior mediastinum and they usually keep their continuity with the thyroid gland in the neck. Nine patients had had an entirely posterior mediastinal intrathoracic goitre and amongst them only 2 had been completely asymptomatic, having only an abnormal mediastinal shadow on routine X-ray.

On 50 patients an operation was undertaken for the removal of the intrathoracic goitre. The last case in this series presented the problem of profuse hæmoptysis associated with cough, sputum, superior vena cava obstruction and paralysed vocal cord. The diagnosis was made of a carcinoma of the thyroid, and on bronchoscopy the neoplastic mass had been seen penetrating the tracheal wall at a level 1 inch above the carina. No further surgical procedure was attempted and the patient had a palliative course of deep X-rays in order to relieve his symptoms. Unfortunately death occurred four weeks later.

Among the other patients 39 had had a low collar incision in the neck which proved to be quite sufficient for the removal of the entire intrathoracic tumour. The complete resection of the tumour is essential as remnants may produce regeneration of the adenomatous goitre. Three patients had presented a history of a previous thyroidectomy in the neck. The low collar incision is adequate for the majority of intrathoracic goitres lying chiefly in the anterior mediastinum. As their blood supply descends from above, ligation of the superior blood vessels enables the back wall of the thyroid to be exposed. The delivery of the intrathoracic portion can be effected with the insertion of the index finger into the mediastinum and disruption within the plane of cleavage of all avascular adhesions which exist in its anterior aspect. These manipulations for the removal of an intrathoracic goitre through the thoracic inlet are hazardous and may produce a total collapse of the wall of the trachea, which must be secured with an endotracheal tube. When the long-standing pressure from the intrathoracic goitre upon the trachea is released the calibre and position usually return to normal.

In 4 patients the collar incision in the neck was combined during the operation with a partial split of the sternum down to the fourth intercostal space. In Keynes' opinion this extra freedom is essential for the safe removal of the intrathoracic goitre. In 5 cases the removal of the goitre was done through a midline incision and split of the sternum. This decision was taken pre-operatively as the thyroid was not palpable in the neck or the episternal notch. Among these patients 3 were suffering from a posterior mediastinal intrathoracic goitre. One goitre was removed through a thoracotomy incision and in 1 patient the intrathoracic portion was freed through the right chest and the operation completed by a collar incision in the neck.

TABLE 1.—OPERATIVE TREATMENT

Collar incision	39
Collar incision and split of sternum	4
Collar incision and right thoracotomy	1
Midline incision and split of sternum	5
Right thoracotomy	1
Bronchoscopy	1

All patients survived operation, although those with malignant infiltration of the thyroid died after four weeks, two, three and six months respectively. All the others had an immediate good recovery, especially those who had been suffering from superior vena cava obstruction. They returned to their work and there has been no evidence of recurrence. Four patients have died from reasons unrelated to the operation. Post-operative complications were few. Collection of fluid in the place of the resected specimen is unpleasant and can be prevented with a small drainage tube at the episternal notch. Accidental tear of one of the pleuræ occurred in 2 patients and artificial pneumothorax was produced. Finally atelectasis of the right upper lobe was seen in 1 patient.

Of possible procedures the collar incision in the neck gives adequate exposure for the removal of the anterior and posterior intrathoracic goitre and we regard it as the procedure of choice. Only for a very enlarged intrathoracic goitre does the split of the sternum give extra safety for the removal of the entire goitre.

Summary

Fifty-one cases of intrathoracic goitres are described, including 9 which have been found lying in the posterior mediastinum. The symptoms, diagnosis and treatment are analysed and discussed.

I am much indebted to Messrs. T. Holmes Sellors, V. C. Thompson, D. Barlow and J. R. Belcher for permission to publish their cases, and their helpful criticism on this paper.

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STOVE-IN CHEST; A NEW METHOD OF INTERNAL FIXATION

J. E. Jacques and W. D. Munro

From the Thoracic Surgical Unit, City Hospital, Nottingham

Stabilisation of the floating segment is of fundamental importance in the treatment of stove-in chest injuries. Ideally, this should achieve the two objects of eliminating paradoxical movement and restoring the shape of the chest to normal. External traction on the floating segment will prevent paradox but is ineffective in maintaining the volume of the chest (Proctor and London, 1955). The individual wiring of multiple rib fractures (Sweet, 1954) appears effective, but must be both complicated and laborious. We describe here a simple method of internal fixation which we have used in two cases of lateral stove-in chest. The method was devised following our experiences with such a case treated by external traction in which we failed to maintain the depressed segment in a reduced position.

Method

The lateral type of injury is characterised by double rows of fractures through a number of ribs on the same side; the anterior fractures may be replaced by costo-chondral dislocations. The depressed segment is almost always confined to the upper seven or eight ribs; the lower ribs, having more lateral resilience, usually remain intact. The majority of cases are of this type.

The principle of the method is to use a single Lane's bone plate passing deep to the floating segment, to which it is not attached, but supporting it in a reduced position. Its lower end is screwed to the intact lower ribs, which afford a fixed point. A long six-hole Lane's plate, bent twice to a cranked shape, is used as shown in Fig. 1 (A and B), which shows the plate attached to a skeleton.

In practice, the operation is not found to be difficult. The position of the patient on the operating table will vary with the position of the floating segment, which is exposed either through a periscapular or a submammary incision. If the pleural cavity is to be opened this is done next, through an intercostal incision which will usually go across the floating segment. This is then closed. We did a thoracotomy in our cases in order to inspect the lung and mediastinum for possible injury, to clear out blood and clot, and to provide drainage of the chest at the most dependent point. A six-hole Lane's plate is placed with its lower end over the intact lower ribs, in the position which it will occupy. The point at which it will dip under the floating seg-

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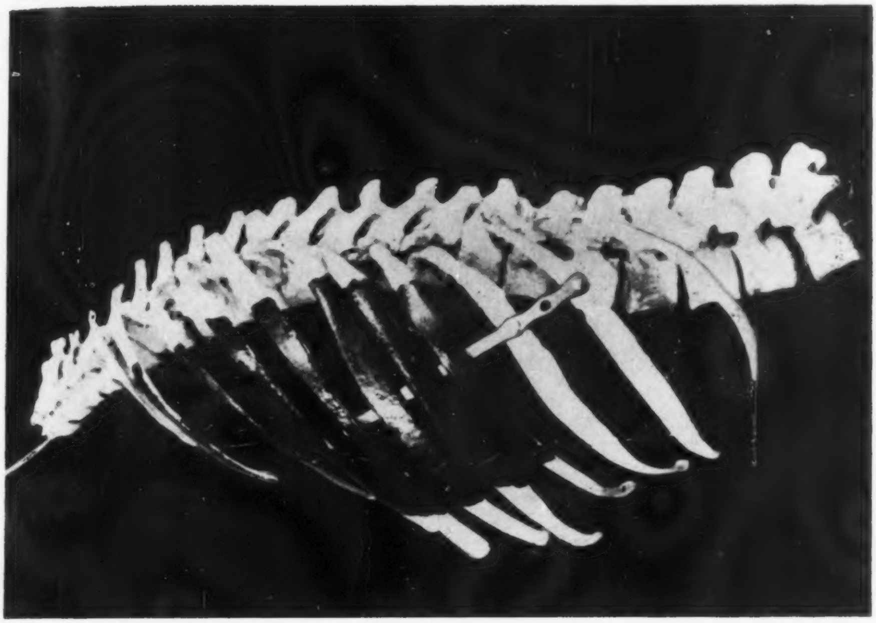

FIG. 1A.—Skeleton with plate attached; the dark areas of the ribs represent the floating segment.

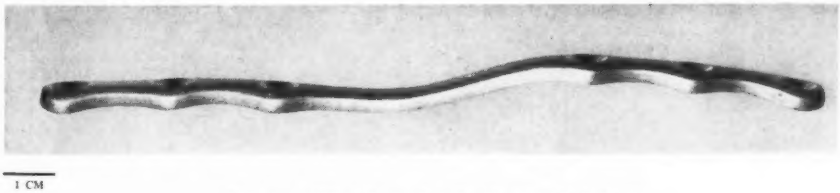

FIG. 1B.—The plate, showing its cranked shape.

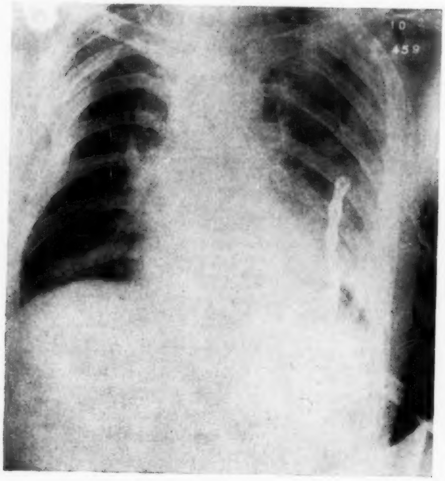

FIG. 2.—Case 1. First day after operation showing plate in position.

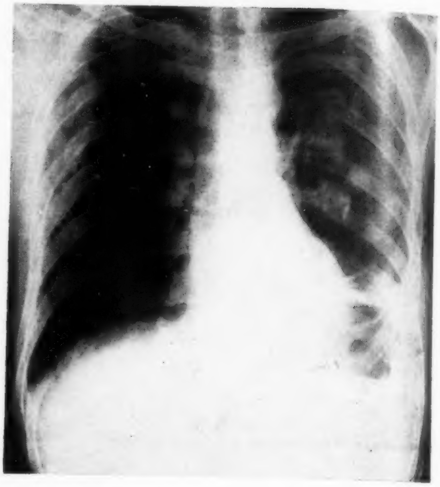

FIG. 3.—X-ray of case 1 at the time of leaving hospital.

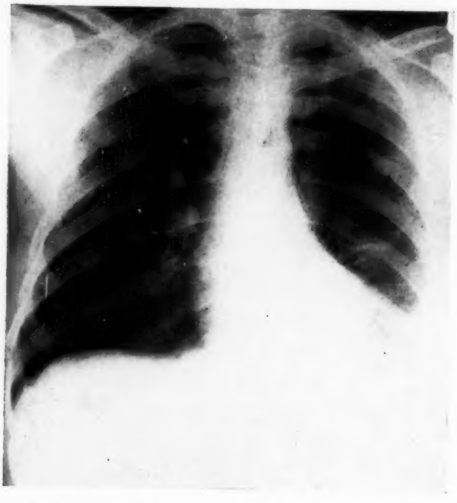

FIG. 4.—X-ray showing end-result on case 2.

ment is marked on it. The plate is then bent twice to its cranked shape with platebenders, the upper bend outwards at the marked point and the lower bend inwards just above the screw-hole through which it will be attached to the uppermost of the intact ribs. The periosteum is then cleared from the under-surface of the lowest rib of the depressed segment, and an extra-pleural tunnel made upwards with the finger. The plate is slid into this, the lower intact ribs are drilled at the points of attachment of the plate, and short screws are inserted.

Eventual removal of the plate is easy. A short incision is made over its lower end under local analgesia, the screws are removed, and the plate slid out.

Case 1. A.G., a man of 26, was admitted after the wheel of a car had passed over his chest. He was conscious, cyanosed, dyspnœic and in considerable pain. X-ray showed double fractures of the left second to eighth ribs, with a hæmo-pneumothorax on this side. On the right there were fractures of the second to eighth ribs posteriorly, and the scapula had been virtually driven into the chest. The right lung was fully expanded. There was marked paradox on the left side but none on the right, for the depressed portion of the chest was covered by the scapula and its attached muscles (Fig. 2).

After insertion of a left anterior intercostal catheter and bronchoscopic suction the patient's condition improved. Operative fixation by the method described was performed under general anæsthesia, some ten hours after injury. Subsequently, paradox was seen to have been completely abolished. Continuous re-accumulation of bronchial secretions necessitated bronchoscopic aspiration hourly during the first five hours. Because of this, tracheostomy was performed, using a cut-down No. 10 endo-tracheal tube. This facilitated tracheo-bronchial toilet, and his condition remained excellent thereafter. He got up on the third day after removal of the drainage tubes; the tracheostomy tube was removed on the fifth day.

The position of the chest wall remained entirely satisfactory. The plate was removed on the twentieth day. At the time of his discharge, four weeks after admission, X-ray (Fig. 3) showed that the depressed segment had united in the fully reduced position.

Case 2. A man of 44 had sustained a left stove-in chest and a dislocated right hip in a car accident. X-ray showed double fractures of the left third to seventh ribs inclusive. On admission he had been somewhat cyanosed, with marked paradox of the left chest. After his hip had been successfully reduced under general anæsthesia, his condition deteriorated; he became progressively more cyanosed and dyspnœic. Following intercostal drainage, bronchoscopy and the application of pad and strapping to the paradoxical chest wall, he improved considerably. Operative fixation was performed as before, except that this time the floating segment was exposed through a submammary incision. The fourth rib was comminuted, and a second small plate was fixed across an additional fracture in it. One supporting plate sufficed to maintain full reduction.

His further progress was satisfactory; the plates were removed on the twentieth day under local analgesia. The maintenance of reduction may be seen in the X-ray taken after removal of the plate (Fig. 4).

Discussion

It is felt that in the treatment of lateral stove-in chest the aim should be not only to preserve life, but also to restore the chest to its previous shape. Whilst external traction will suffice to prevent paradox it is not possible to maintain complete reduction of the depressed segment. The simple method of internal fixation described here completely eliminates paradox and obtains an end result which is almost perfect, without the complications of individual wiring or plating of multiple fractures. Two cases only are described, but we consider that the principle has been established; the depressed segment can be maintained in a reduced position with a single supporting plate.

Summary

A new method of fixation of the floating segment in a lateral stove-in chest is described. This has been found to give an excellent functional result.

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SPUTUM-POSITIVE COALWORKER'S PNEUMOCONIOSIS AND DRUG THERAPY

By R. L. Sadler

From the Chest Clinic, Mexborough, Yorkshire

The hypothesis that progressive massive fibrosis (P.M.F.) in pneumoconiotic lungs is actually a modified form of tuberculosis is widely accepted. It was demonstrated by Mann (1951), however, that pulmonary tuberculosis in an unmodified form also exists in the presence of simple pneumoconiosis: the distinction was justified by the different progression shown by opacities which he diagnosed as unmodified tuberculosis compared with those which he classified as P.M.F. Cochrane *et al.* (1956) believe that such a differentiation is rarely possible where the degree of simple pneumoconiosis is more advanced than Category 1 of the Pneumoconiosis Research Unit classification (Davis *et al.*, 1948).

In the tuberculosis registers of this clinic, covering eight years prior to June 1956, 27 mineworkers with a certified pneumoconiosis disability have been traced; all have had one or more sputa containing tubercle bacilli and all but 3, pulmonary cavitation on X-ray.

Cases have been grouped by radiographic appearances of the lung fields. Group O comprises cases with Category 1 simple pneumoconiosis together with unmodified reinfection type tuberculosis. Groups A, B and C include cases which show these respective categories of P.M.F. in the pneumoconiosis classification mentioned above.

The cases were observed for a mean period of slightly less than four years following their admission to the tuberculosis register, and their condition at the end of this time is summarised in Table 1. During the period of observa-

TABLE 1

	Group O	*Group A*	*Group B*	*Group C*
Mean age at notification	46·6 ± 4·3	55·1 ± 6	59·9 ± 9·3 *All fatal cases:*	55·6 ± 2 57 ± 2·2
Cases	5	8	8(3)	1(2)
Sputum conversion	5	3*	0(2)*	0
Cavitation: closed	5	1	0	0
static or increased..	0	6	8(1)	1(2)
Clinical condition: improved ..	5	2	0	0
static or worse	0	6	7(2)	0
Died	0	0	1(1)	1(2)

*Cases who had a positive sputum on one occasion only.
Figures in parenthesis indicate untreated cases.

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tion cases received combined drug therapy with streptomycin, isoniazid and P.A.S., in various standard courses, for a minimum of nine months, excepting 5 cases in Groups B and C who had no significant treatment.

In Group O the response to drug therapy was that commonly observed among cases of open pulmonary tuberculosis, where pneumoconiosis is not a complication. Cavity closure and other radiological improvements were clearly evident in all cases within six months of beginning treatment. Sputum conversion had occurred within nine months in one (Case 2) and within three months in the other 4 cases. Dyspnœa with exertion (grade 1 and grade 2) remained in 2 cases, but otherwise there were no residual pulmonary symptoms. All became sufficiently well to do light work.

The following cases are examples from Group O:

Case 1. Collier, aged 40. November 1954, history of cough, sputum, hæmoptyses for one month. Sputum smears positive. X-ray showed cavity (3 cm.) and heavy tuberculous mottling in left upper zone. (Decision about presence of pneumoconiosis not confirmed by Pneumoconiosis Panel until six months treatment completed.) B.S.R. (Westergren) 21 mm. one hour. Daily streptomycin, isoniazid and PAS for six months in sanatorium and thrice weekly for nine months at home. Sputum permanently converted after two months' therapy. On discharge from sanatorium he was symptomless, had gained 18 lb., B.S.R. was 2 mm. one hour. May 1955, X-ray showed considerable resolution of tuberculosis infiltration and cavity not discernible, with Category 1 pneumoconiosis. Fit for light work two years from commencing therapy.

Case 2. Coal face worker, aged 45. November 1955, history of cough, sputum, hoarseness, loss of weight for three years. Sputum smears positive. X-ray showed cavity (5 cm.) and tuberculous infiltration in apical segment of right lower lobe with Category 1 pneumoconiosis. Refused sanatorium and bed rest. At home had thrice weekly streptomycin, isoniazid and PAS for sixteen months. After three months' treatment no pulmonary symptoms, gained 15 lb., and cavity closed. Sputa not re-examined before nine months' treatment, when smears and cultures repeatedly negative. At this date tuberculous infiltration represented by a small round focus at right hilum. Fit for light work twenty months from commencing therapy.

In contrast there was in Groups A, B and C little evidence of any response to treatment. During the period of observation two deaths occurred among the treated (and three among the untreated) cases. The fatal cases were among those with the greatest extent of disease as seen radiologically; and it is obvious that before other factors in survival, such as drug therapy, can be assessed, cases have to be classified according to disease extent. The size and method of selection of the present sample do not permit this.

Of the surviving cases, 12 had persistently positive sputa during and after therapy, which was continued for periods ranging from nine months to three years. In one case tubercle bacilli remained sensitive to all three drugs after two years' treatment, but in 4 others resistance to one or all drugs had developed earlier than this. A case in which a single positive is followed by a number of negatives is not necessarily an instance of sputum conversion, for the bronchial communication with P.M.F. cavities may be intermittent (Kilpatrick *et al.*, 1954). This is illustrated in two of the untreated cases, where solitary positive smears were reported in the middle of series of 8 and 13 respectively, of negative smears and cultures (examined at intervals over several years).

Further, no evidence of cavity closure or other radiological improvement was evident in Groups A, B and C, apart from that detailed in Case 4 below. Indeed, only the following two cases of these groups showed any clear evidence of clinical or radiological response to therapy.

CASE 3. Collier, aged 47. Contact X-ray March 1953 (wife had open tuberculosis) showed Category 3 simple pneumoconiosis. X-ray May 1955 showed also an "A" shadow in right lung. At this date he complained of cough, sputum, lassitude for several months, but the chest had no significant physical signs. B.S.R. 5 mm. (Westergren). Sanatorium six months. On discharge no symptoms relevant to pulmonary disease and he had gained 16 lb. All sputa negative after initial positive smear. X-rays remained unchanged after May 1955. Had streptomycin, PAS and isoniazid daily for twenty-one weeks and then PAS and isoniazid daily for further twelve months. Fit for light work eighteen months from commencing therapy.

CASE 4. Mining fitter, aged 45. Mass Radiography X-ray March 1955 showed Category 3 pneumoconiosis with "A" shadows both upper zones and cavity (3 cm.) below the right "A" shadow. Complained of cough and dyspnœa (grade 1) of uncertain duration. Chest showed no physical signs of note. B.S.R. 11 mm. one hour (Westergren). Sputum positive on culture (second specimen). Sanatorium five months. All sputa negative after initial positive culture. On discharge from sanatorium: he had gained 18 lb., had no cough but dyspnœa as on admission, B.S.R. 2 mm. X-ray, March 1956, showed closure of cavity but no other changes. Had streptomycin, PAS and isoniazid daily for two months and thrice weekly for three months, then PAS and isoniazid daily for five months when discontinued because of nausea. Fit for light work two years from commencing therapy.

Discussion

The small group of cases with unmodified pulmonary tuberculosis responded to combined drug therapy with general and radiological improvement and with early sputum conversion. In contrast, the results with sputum-positive P.M.F. cases were quite unpromising in these respects.

Two of the treated P.M.F. cases died during the period of observation. This fatality rate compares with one death noted in two and a half years among 12 similar cases of Cochrane *et al.* (1955). Other authors have reported considerably higher death rates: 70 per cent. in two years (Theodos and Gordon, 1952), 33 per cent. in one year (Cohen, 1953) and 88 per cent. in two years (Kilpatrick *et al.*, 1954); but these samples were not unselected ones. Such divergent findings, moreover, reflect the necessity for first classifying cases of P.M.F. according to their extent of disease before assessing survival rates. It is interesting to recall how greatly mortality rates in pulmonary tuberculosis were clarified when the importance of radiological extent of disease was realised (Foster-Carter *et al.*, 1952).

In other series of sputum-positive P.M.F. cases, drug therapy appears to have been no more successful than in the present group in achieving either sputum conversion or cavity closure. Cohen (1953) found no sputum conversions in 18 and Carpenter *et al.* (1956) in only one of 12 cases; Courtois (1956) obtained permanent conversion in 2 of 10 cases. No cavity closure was found among the cases of Boselli and Lusardi (1950) or of Cohen (1953). Courtois (1956) noted closure in 1 of 10 treated cases.

Two only of our P.M.F. cases showed some response (clinical or radiological) to drug treatment. Both these cases, however, had only early "A" shadows and the differentiation of these from the shadows of unmodified pulmonary tuberculosis is notably difficult (Cochrane *et al.*, 1956).

In deciding on the line of treatment for sputum-positive P.M.F. cases the following considerations are relevant: where the fibrosis is of greater degree than Category A there is unlikely to be clinical improvement or sputum conversion with drug therapy; and persistence with this treatment may lead to chronic infectious cases becoming also sources of drug-resistant tubercle bacilli.

Summary

Five cases with unmodified pulmonary tuberculosis in the presence of simple pneumoconiosis responded clinically and radiologically to combined drug therapy.

In contrast, little response to therapy was evident in 17 cases with positive sputa and progressive massive fibrosis. Of these cases 2 improved and 2 died, and none of the remainder showed cavity closure or a definite sputum conversion. Some cases developed drug-resistant tubercle bacilli.

The importance of classifying cases with progressive massive fibrosis by disease extent, before assessing fatality rates, is stressed.

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THE LUNG OF EXPERIMENTAL MAMMALS (GUINEA PIG)

By S. Engel

Department of Anatomy, The Royal College of Surgeons of England

The mammalian respiratory tissue is, generally speaking, acinar in structure; that is to say, the lung is composed of numerous small units, acini, the structure of which is basically the same in small and large mammals.

It is the purpose of this paper to describe some particular features in the pulmonary structure of the guinea pig which may bear upon the results of certain experiments.

In very small mammals, mice for instance, the respiratory elements are little differentiated, being narrow cylindrical tubules studded with minute flat alveoli. The acinus of the rat is more complex and shows all the features met with in the acini of larger mammals. In the guinea pig it is obvious that the respiratory tissue is primitive in structure, particularly in view of the size of the animal (weight 300 to 500 grammes).

The Structure of the Acini

The respiratory elements of the guinea pig are small and cylindrical in shape. The tuft of tubules arising from a terminal bronchiolus consists of dividing and redividing tubules (Fig. 1), all of which are fairly uniform in width and shape. Generally speaking, the arrangement of the tubules is similar to the system of the intra-acinar tubules in the customary acinus, but neither bronchioli respiratorii, ductus alveolares nor sacculi alveolares are definitely recognisable; the acinar tuft is a system (Fig. 1), rich or poor, of cylindrical, badly alveolated tubules. The " acini " vary in size and in the kind of ramification but remain cylindrical from the bronchiolus to the peripheral end. Finally they split dichotomically into two short branches or pairs of branches, the length of which is insignificant as compared with the whole cylindrical system (Plate XXV, Figs. 2, 3).

The structure of the respiratory tissue has been dealt with in some detail in view of the fact that function is largely dependent on anatomical structure. The respiratory surface per c.c. of primitive lung tissue is bound to be much less than in a lung with highly differentiated acini. The lung of the guinea pig may be adapted to the particular needs of the animal, but it is most unsuitable for experiments on the respiratory function in various conditions.

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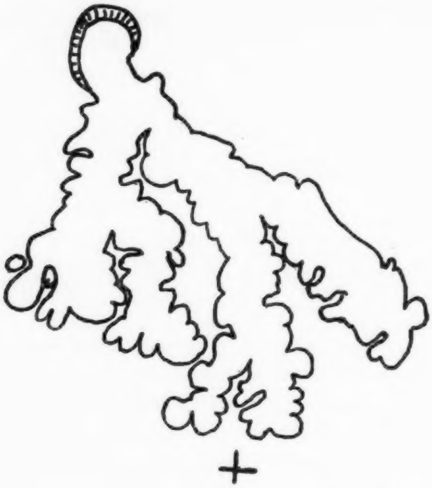


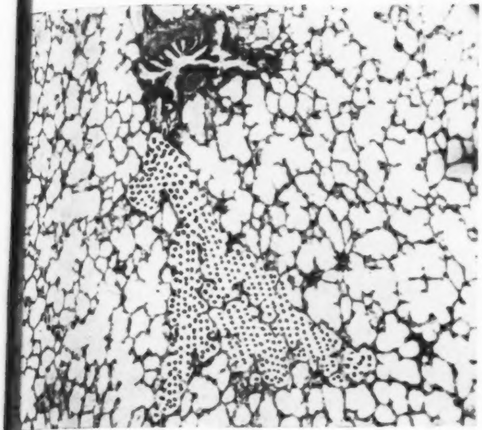
FIG. 1.—Camera lucida tracing of part of an acinus showing the primitive shape of the tubular elements. The place marked (+) points to the final redivision by dichotomy. × 100.

THE BRONCHIAL TREE

The bronchial tree of the guinea pig is peculiar in its mural structure and this fact also may bear on the use of the animal for experiments. These peculiarities are the more important as the pulmonary artery also shows similar structural peculiarities. In the bronchial tree cartilage advances much farther than in the rat, which may again serve for comparison. Whereas in the rat only the main bronchi contain cartilage, in the guinea pig it advances to three or four generations. This is remarkable enough, but still more surprising is the excess of muscle in the bronchial tree (Plate XXV, Fig. 4) as well as in the branches of the pulmonary artery. In most mammals muscle is not a prominent feature of the pulmonary structure, but serves as motor to the gliding mucous membrane in the bronchi and as a stabilising element in the bronchioli. In the guinea pig the muscle is excessively strong in the bronchial tree, especially in the small branches. It decreases gradually in the air passages towards the periphery but remains more or less adapted to the bronchial or bronchiolar calibre (Plate XXVI, Figs. 5, 6). In the pulmonary artery the muscle does not form a uniform layer but forms intumescences, and remains strong throughout.

Both the muscle in the bronchial tree and in the pulmonary artery will, by contraction, arrest the flow of air or blood or work simultaneously. Small or large portions of the lung can thus be put out of function. The muscle may serve to regulate the respiration physiologically, but may also respond to pathological stimuli or irritants. The guinea pig is, therefore, unsuitable as an experimental animal in the study of respiratory peculiarities and/or of stress and

PLATE XXV



s. 2.—Photomicrograph containing part (dotted) of an inus from the terminal bronchiolus (top) to the periphery. ×60.

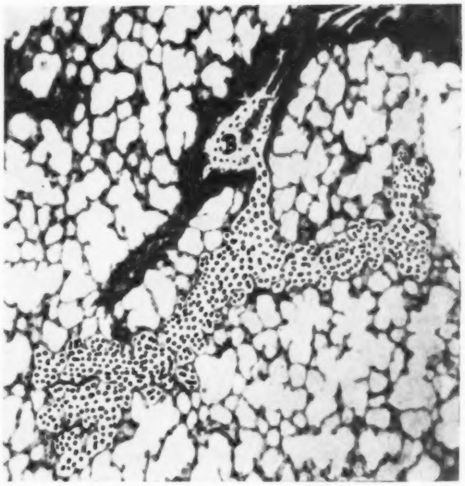


FIG. 3.—Photomicrograph of an aciner arrangement different from that of Fig. 2. The terminal bronchiolus is marked (B), the respiratory elements are dotted. ×65.

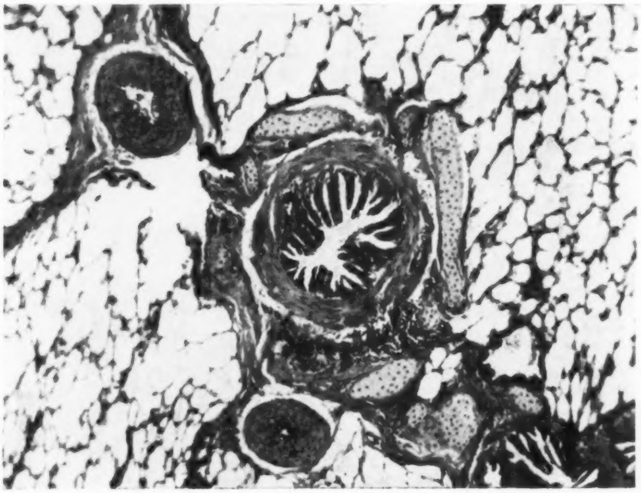


FIG. 4.—Photomicrograph showing a cross-cut bronchus (0·3 mm. diameter from base to base of epithelium). The photograph includes two cross-cut branches of the pulmonary artery. Muscle is conspicuous in the bronchus and in the minute branches of the pulmonary artery. Remarkable also are the cartilages of this small bronchus. ×65.

PLATE XXVI

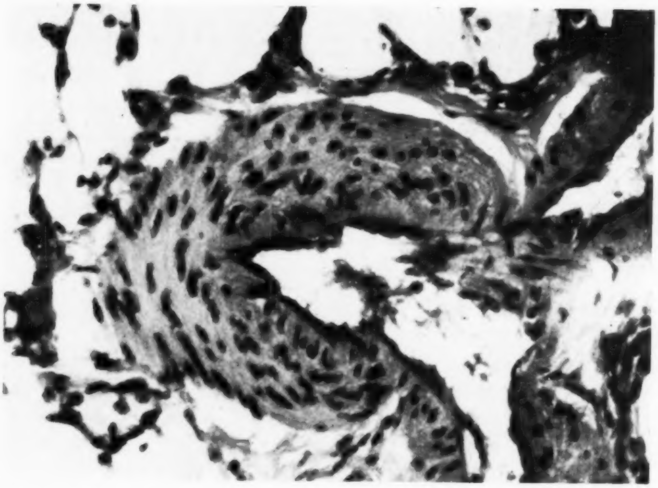


FIG. 5.—Cross section through the nodular muscle of a small branch of the pulmonary artery from which two smaller branches originate. They are cut longitudinally and their muscle also is strong. × 400.

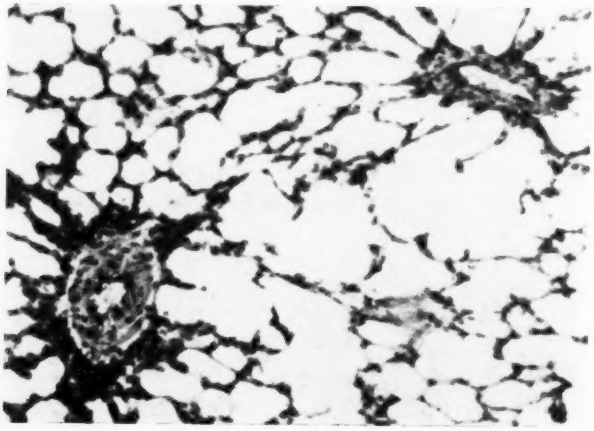


FIG. 6.—Cross sections through two minute branches of the pulmonary artery, the musculature of which is thickened. × 100.

shock. A warning example is supplied by experiments, conducted many years ago, on the question whether some portions of the lung are collapsed or not in normal respiration. The positive result may be true in the guinea pig, but not necessarily in other mammals with less muscle in the air-ways and vessels. This statement does not contradict the well-known fact that parts of the mammalian lung, in man for instance, are little used in normal respiration, being kept as a reserve for hard breathing periods.

In spite of all this, it is interesting to know that two animals which are highly sensitive to the tubercle bacillus are also distinguished by containing an excess of muscle in their lungs, namely the guinea pig and ox.

Summary

While studying the comparative anatomy of mammalian respiratory tissue certain peculiarities in the lung of the guinea pig, an animal so frequently used for experiments, were noted. The respiratory tissue is primitive and the bronchial tree as well as the pulmonary artery contains an excess of musculature. The conclusion is reached that the guinea pig should not be used for certain experiments.

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A COMPARISON OF PROTEINS IN SERUM AND PLEURAL FLUID

By M. D. Watkins

From the London Chest Hospital

Introduction

The diagnostic problem of a pleural effusion occurring in elderly patients is one of considerable clinical importance. In recent years the rise in the number of cases of tuberculosis diagnosed for the first time in elderly people, together with the large number of cases of malignant disease in this age group, makes the diagnosis of a pleural effusion an urgent necessity. Forty-one of the fifty-two cases in the present series were over the age of 40 years, and of these half were neoplastic in origin. Table I shows the age distribution of cases and the ætiological variations over the age of 40 years. The cases of post-operative effusion were included in the series for the purpose of comparison.

Table I

Age distribution of cases:			
Total No. of cases	52		
No. of cases of			
Neoplasm	21	Average age 57·8 yrs.	Range 45-80 yrs.
Tuberculosis	14	,, ,, 36·7 yrs.	,, 19-64 yrs.
Post-Infective	8	,, ,, 47·3 yrs.	,, 3-71 yrs.
Cardiac Failure	3	,, ,, 73·3 yrs.	,, 64-82 yrs.
Post-operative	6	,, ,, 52·3 yrs.	,, 28-74 yrs.
Cases of effusion over 40 yrs.:			
Total No. of cases	41 — 79%		
No. of cases of			
Neoplasm	21 — 51%		
Tuberculosis	5 — 12%	Non-neoplastic 37%	
Post-Infective	7 — 17%		
Cardiac Failure	3 — 8%		
Post-operative	5 — 12%		

Many attempts have been made to differentiate biochemically between pleural effusions, using amino-acid composition (Sandler, 1956); glucose content (Foord, Youngberg, and Wetmore, 1929; Gelenger and Wiggers, 1949; Calnan, Winfield, Crowley and Bloom, 1951); hyaluronic acid (Cutinelli, 1951); pseudocholinesterase levels (Polimeni and Turitto, 1951); leukotaxine (Truozzi, 1947); but no method has proved reliable for routine use. The protein concentration and composition has also been investigated (Felder, 1953; Karges and Mond, 1954; Keller, 1954; Münz, 1954; Hitze, 1955; Peiper and Heine, 1956; Zinneman, Johnson and Lyon, 1957), but there has been considerable difference of opinion as to its value. Some authors

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(Keller, 1954; Karges and Mond, 1954; Zinneman, Johnson and Lyon, 1957) state that the protein composition in pleural fluid resembles that of serum, except that the proportion of albumen is greater in pleural fluid. Other workers, (Hitze, 1955; Shaw and Brews, 1956) however, suggest that there may be certain differences in the composition of pleural fluid protein between malignant and inflammatory effusions. Hitze felt that by using suitable quotients two types of effusion could be differentiated, although this was only a preliminary series. Shaw and Brews noted in two cases of carcinoma of the bronchus with effusion that the α_2 globulin in the pleural fluid was strikingly low in contrast to the high α_2 globulin in the serum.

The present investigation was designed to compare the proteins in serum and pleural fluid using the technique of paper electrophoresis, and to see if it were possible to distinguish between pleural effusions in various diseases.

CLINICAL MATERIAL AND METHODS

Samples of serum and pleural fluid were obtained at the same time from 52 cases of pleural effusion. Pleural fluid which was frankly blood-stained or purulent was discarded immediately. Serous fluid which was subsequently found to be infected with organisms other than tubercle bacilli, or in which the total protein content was less than 2 g./100 ml., was also discarded. Technical difficulties made it advisable to discard fluid of low protein content, but this was necessary in only 3 cases in the present study, the effusion in each case being due to cardiac failure. Fluid and serum were obtained where possible before treatment was begun. The pleural fluid was collected in plain bottles and allowed to clot. It was used as soon as possible after withdrawal, but where there was any delay it was kept refrigerated at 4° C.

TABLE II.—ÆTIOLOGY OF PLEURAL EFFUSIONS

Neoplastic	21 cases	Carcinoma of bronchus	15
		Secondary carcinoma (breast)	2
		Hodgkin's disease	1
		Leukæmia (lymphatic)	1
		Probable Ca bronchus	2
Tuberculosis	14 cases	Radiological parenchymal disease	6
		No radiological parenchymal disease	8
Post-infective (including 2 infected cysts)			8
Cardiac failure	3 cases	Hypertensive heart disease	2
		Mitral stenosis	1
Post-operative	6 cases	Benign tumour	1
		Valvotomy, poundrage	5

The diagnosis in 19 of the 21 cases of neoplastic disease was confirmed by histology. In the other 2 cases, the bronchoscopic appearances were suggestive, but no biopsy was obtained. In the tuberculosis group 8 cases had positive evidence of active disease (sputum tests, pleural biopsy) and in the other 6 cases the X-ray appearances and clinical course of the illness were considered diagnostic.

BIOCHEMICAL METHODS

Total protein estimation was carried out by a micro-Kjeldahl technique using a nitrogen conversion factor of 6·25.

Paper electrophoresis of serum and pleural fluid was carried out simultaneously using a horizontal open-strip method on Whatman No. 4 filter paper in 0·06 M Barbitone buffer *p*H 8·6 at 60V and 2·5m A for 16 hrs.

The strips were dyed in aqueous brom-cresol-green and scanned in a reflectance densitometer. Over the range of protein concentrations encountered in this work, the densitometer response was directly proportional to the protein concentration (Franglen, 1957). The resultant scan was analysed by division into its constituent parts by reflection across the medians, and by subsequent planimetry. The relative concentrations of the protein fractions were then calculated.

RESULTS

On comparison of the electrophoretic strips of serum and pleural fluid in each case, the most striking feature was the marked reduction in α_2 globulin in the pleural fluid in the majority of cases of neoplastic effusion in contrast to the

TABLE III

*Serum Analyses**

Cases	*Total Protein*	*Albumen*	*Globulins*			
			α_1	α_2	β	γ
Normal (20 cases)	6·90 ±0·08	4·71 ±0·05 (68·3%)	0·23 ±0·01 (3·3%)	0·42 ±0·01 (6·1%)	0·77 ±0·03 (11·1%)	0·78 ±0·03 (11·2%)
Neoplastic (21 cases)	6·40 ±0·11	3·71 ±0·12 (57·8%)	0·36 ±0·03 (5·5%)	0·67 ±0·03 (10·5%)	0·78 ±0·04 (12·2%)	0·86 ±0·05 (13·5%)
Tuberculous (14 cases)	6·60 ±0·17	3·72 ±0·14 (56·4%)	0·40 ±0·04 (6·1%)	0·74 ±0·03 (11·2%)	0·79 ±0·04 (12·0%)	0·91 ±0·05 (13·8%)
Others (17 cases)	6·55 ±0·15	3·86 ±0·24 (58·9%)	0·29 ±0·03 (4·4%)	0·60 ±0·05 (9·2%)	0·75 ±0·05 (11·5%)	1·03 ±0·13 (15·7%)
Non-neoplastic (31 cases)	6·58 ±0·11	3·81 ±0·15 (57·9%)	0·34 ±0·02 (5·3%)	0·68 ±0·05 (10·3%)	0·78 ±0·04 (11·8%)	0·97 ±0·06 (14·7%)

*Pleural Fluid Analyses**

Cases	*Total Protein*	*Albumen*	*Globulins*			
			α_1	α_2	β	γ
Neoplastic (21 cases)	3·80 ±0·17	2·35 ±0·15 (61·8%)	0·19 ±0·02 (5·0%)	0·24 ±0·03 (6·5%)	0·49 ±0·03 (13·2%)	0·51 ±0·03 (13·4%)
Tuberculous (14 cases)	4·04 ±0·24	2·31 ±0·16 (57·2%)	0·26 ±0·02 (6·4%)	0·38 ±0·04 (9·4%)	0·49 ±0·04 (13·1%)	0·56 ±0·03 (13·8%)
Others (17 cases)	3·94 ±0·16	2·36 ±0·15 (59·9%)	0·18 ±0·01 (4·5%)	0·33 ±0·03 (8·4%)	0·42 ±0·02 (11·6%)	0·62 ±0·07 (15·7%)
Non-neoplastic (31 cases) (Tuberculous and others)	3·96 ±0·13	2·33 ±0·11 (58·8%)	0·22 ±0·01 (5·6%)	0·36 ±0·02 (9·1%)	0·45 ±0·02 (11·4%)	0·58 ±0·03 (14·6%)

* Mean Values in g./100 ml. and standard error of mean.

PLATE XXVII

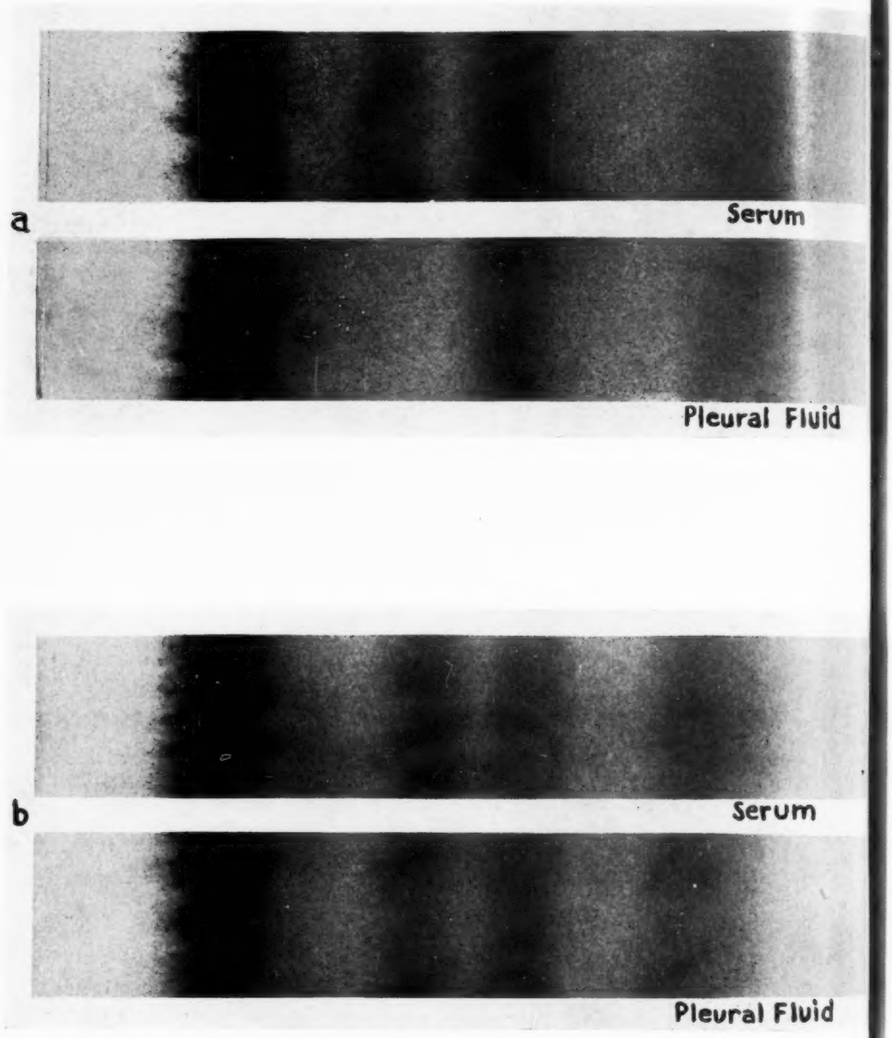
a
Serum
Pleural Fluid
b
Serum
Pleural Fluid

FIG. 1.—Showing electrophoresis of serum and pleural fluid in (*a*) Carcinoma of bronchus (*b*) Pulmonary Tuberculosis.

To face p. 173

high α_2 globulin of the corresponding serum. In the remainder of cases the high α_2 globulin in the serum was reflected in the pleural fluid (Fig. 1). These observations were confirmed by analysis of the strips, and the results are shown in Table III.

SERUM ANALYSIS

The mean values for both total protein and albumen concentrations in all groups were markedly reduced. In all groups the α_2 globulin levels were raised above normal and in the non-neoplastic groups the γ globulin was also raised. These changes are statistically significant. ($P<0{\cdot}01$ in all cases). In the group of neoplastic cases the mean γ globulin value was also raised, but there was a wide variation in concentration (0·57-1·73 g./100 ml.) and the change was not significant.

PLEURAL FLUID ANALYSIS

Total protein concentration ranged between 2·1-5·2 g./100 ml. and no difference was found between the various groups. The mean percentage albumen in pleural fluid was slightly higher than that of the corresponding serum in all groups, but the difference was very small and not significant. The most important variations lay in the α_2 globulin values. The mean α_2 globulin level in the pleural fluid of neoplastic effusions was significantly lower than the value for all other groups ($P<0{\cdot}01$). The other globulin fractions show no significant variations between the groups.

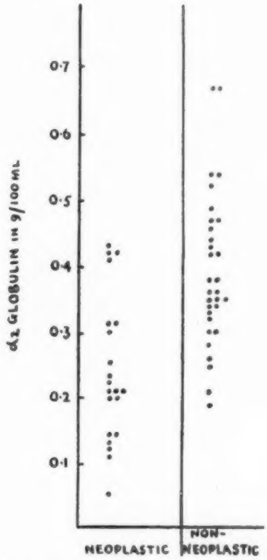

FIG. 2.—To show levels of α_2 globulin (g./100 ml.) in pleural fluid in neoplastic and non-neoplastic effusions.

Comparison of Serum and Pleural Fluid

Although the mean values of α_2 globulin in pleural fluid of neoplastic effusion is significantly lower than in other effusions, attempts to use this value alone are disappointing, since the overlap is too great for this purpose (see Fig. 2). This is not surprising when the wide range of total protein concentration of the pleural fluid in these cases (2·4-5·2 g./100 ml.) is taken into account. Moreoever the marked difference in the electrophoretic strips lay in the contrast between the relatively high α_2 globulin in the serum and the lower α_2 globulin in corresponding pleural fluid, rather than in the absolute levels. Since both from visual examination of the electrophoretic strips and from subsequent analysis of its component parts the β globulin fraction remained the most constant throughout the serum and pleural fluid of all groups, the changes in the α_2 globulin were related to the β globulin. The results are plotted in Fig. 3. From this it appears that the majority of neoplastic effusions can be separated from other effusions using the α_2/β ratio.

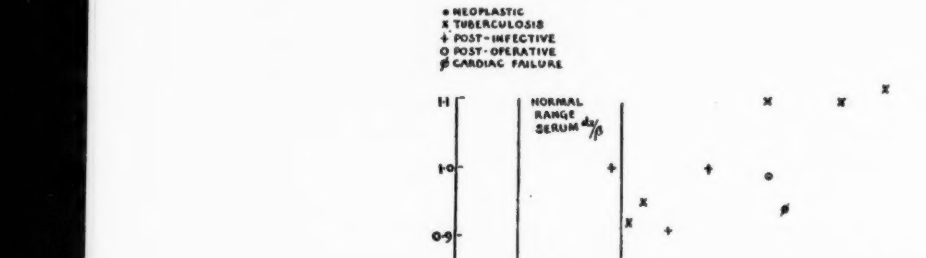

FIG. 3.—To show relationship between α_2/β (g./100 ml.) in serum and pleural fluid.

Discussion

The difficulty of comparing results from different laboratories is greatly increased by the wide variety of techniques used in paper electrophoresis, and emphasises the importance of establishing a normal range for each particular technique and apparatus used. Once this is established, and reproducible results can be obtained, then comparison of the normal and abnormal under the conditions specified will be of considerable value.

Changes in serum proteins in disease, including both cancer and tuberculosis, have been the subject of extensive investigation (Gutman, 1948; Mider, Alling and Morton, 1950; Seibert, Seibert, Atno and Campbell, 1947; Flynn, 1954; Gilliland, Johnston, Stradling and Abdel-Wahab, 1956; Shaw and Brews, 1956), and the values in the present investigation are in broad agreement. The fact that the total serum proteins were markedly reduced in the majority of cases of pleural effusion, and not only in diseases already known to be associated with such a fall, was thought to be due in part to loss of protein into the pleural cavity.

Changes in pleural fluid protein have also been studied, and it seems that the fact that some workers (Karges and Mond, 1954; Keller, 1954; Münz, 1954) have suggested that protein in pleural fluid resembles that of serum except in the relative proportions of albumen and globulin has led other workers (Zinneman, Johnson and Lyon, 1956) to examine pleural fluid without reference to the corresponding serum except in a very few instances.

From the present study it appears that when the protein pattern of pleural fluid is considered in relation to the serum, two main groups emerge:

1. In which the pleural fluid closely resembles the serum.
2. In which there is a marked discrepancy between the a_2 globulin in serum and pleural fluid.

The majority of cases of neoplastic effusion fall into the second group, but the division is not absolutely clear cut. In some instances effusions associated with tuberculosis or other infection lie in the second group, whereas in a few cases effusions due to neoplasm do not show these changes.

It is possible that in those cases of neoplastic disease with effusion in which the alterations in a_2 globulin are absent or not marked, the effusion is not primarily associated with the neoplastic process, but is secondary to infection or minor arterial embolism (Hanbury, Cureton and Simon, 1954). However, at present, no explanation can be offered for those cases of non-neoplastic disease which fall into the second group.

In the present state of knowledge there is no known distinction between the factors governing production and resorption of pleural fluid in different diseases. The production of abnormal amounts of fluid depends on increased capillary permeability, with direct leakage from the blood stream into the pleural cavity (Menkin, 1953), while blockage of lymphatic channels and deposits of fibrin on the pleura hinders its removal. Under these circumstances it seems unlikely that mechnical factors can explain the changes found in this study since the α_2 globulin molecule is relatively small compared with β or γ globulin.

Zinneman, Johnson and Lyon (1956) found a good correlation between mucoprotein and α_2 globulin content of pleural exudates, and it was felt that this might provide a clue to the changes found in neoplastic effusions. However, a survey of the relation between protein-bound polysaccharides and α_2 globulin in 32 cases in the present series gave no further information.

Although no explanation is at present available to account for the alterations in α_2 globulin in the serum and pleural fluid of cases of neoplastic disease, it is suggested that they are sufficiently constant to be considered as an aid in the differentiation of certain cases presenting with a pleural effusion.

Summary

A comparison was made between the proteins in serum and pleural fluid in 52 cases of pleural effusion using the technique of paper electrophoresis.

The results showed a marked difference in the proportion of α_2 globulin present in the serum and pleural fluid in the majority of cases of pleural effusion associated with neoplastic disease. It is suggested that these changes might be used as an aid in the differential diagnosis of cases of pleural effusion.

My thanks are due to the Physicians of the London Chest Hospital and St. Stephen's Hospital for specimens of serum and pleural fluid from patients under their care.

I should also like to thank Dr. K. F. W. Hinson for his kind encouragement and advice in this work, which was done while in receipt of a grant from the Research Fund of the Hospitals for Diseases of the Chest.

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REVIEWS OF BOOKS

The John Alexander Monograph Series. Surgical Management of Pulmonary Tuberculosis. Edited by JOHN D. STEELE. Illinois: Charles C. Thomas. Pp. 213. 72s.

This monograph is remarkable in many ways. Firstly, it is written expressly as a memorial and a tribute to the late John Alexander by a group of American surgeons, all distinguished in their own right, and all of whom, at one time, were trained by and were residents of Dr. Alexander. What greater tribute could be paid, and how well deserved it is will be agreed to by all who knew and admired this charming and outstanding person.

It appears that this monograph is the first of a series which eventually will cover the whole field of thoracic surgery. Dr. Steele points out, in the preface, that this choice of the surgical management of pulmonary tuberculosis for the first volume was, in itself, a tribute to the primary interest of John Alexander, whose pioneering work in this field is well known, not only in our own country but throughout the world. All aspects of the problem are dealt with clearly and succinctly. Naturally not everyone will agree with all the views promulgated, views which even within the confines of the book are sometimes divergent, but that, as the editor points out, of necessity must be, when there are a number of different contributors.

The book itself is of convenient size, the type very clear, the general layout very good, and the reproductions are excellent.

Cameron Haight draws a sensitive and faithful portrait of his old chief with whom he worked in such close and harmonious contact for so many years.

The first chapter by John Steele recalls the two books " The Surgery of Pulmonary Tuberculosis " and " Collapse Therapy in Pulmonary Tuberculosis," which were to have been followed, but for John Alexander's untimely death, by the third book which was to have been called " The Surgical Management of Pulmonary Tuberculosis." This chapter is largely compiled of direct quotations from the two former books and forms a warm link with the present volume.

Each of the articles is of a high standard and reflects accurately prevailing thought in the United States on this problem, which still remains an important one.

To particularise as to the various contributions is a little invidious, but mention must be made of that by Dr. John Jones on the historical aspect of lung resection as a definite form of treatment, and also Dr. Max Chamberlain's section on segmental resection.

This is a book which all who are interested in the field of tuberculosis and chest medicine in general will wish to have in their libraries. The succeeding volumes, if they reach the high standard set by this one, will be awaited with lively anticipation.

CLEMENT PRICE THOMAS.

Recent Trends in Chronic Bronchitis. Edited by NEVILLE C. OSWALD, T.D., M.D.(Cantab.), F.R.C.P. London. Pp. 199, Figs. 74, 8 in colour. Lloyd-Luke (Medical Books) Ltd. 1958. 30s. net.

One of the difficulties in writing a book on " Chronic Bronchitis " is to know what to include under this title. Dr. Oswald considers that " there is no clear line of differentiation clinically between bronchitis, asthma and emphysema," a view which, I think, is not held by all physicians.

The chapters entitled "Mortality and Morbidity," "Clinic Pattern," "Mucus" and "Clinical Management" are written by Dr. Oswald, and these will be of greatest interest to the physician. Little light is thrown on the ætiology of the disease. The place of antibiotic therapy and its indications, according to the views of the author, is outlined. In the majority of cases we still have to fall back upon the well-tried remedies, a sedative cough mixture, the Brompton hot water medicine, and antispasmodics.

Dr. Lynne Reid has contributed a chapter on "The Pathology of Chronic Bronchitis." She considers that hypersecretion of mucus and damage to lung periphery are two essential phases of chronic bronchitis. Dr. G. Simon describes the radiological appearances, which in the early stages are slight or non-existent. This chapter is well illustrated. Bacteriology is discussed by Dr. J. Robert May. He emphasises the tendency of infection to relapse after chemotherapy, due to the persistent growth of the *H. influenzæ*. A very scholarly and interesting account of "Air Pollution and Chronic Bronchitis" has been written by Dr. Patrick J. Lawther. Tests for "Disturbances of Respiratory Function" are the subject of a chapter by Dr. David V. Bates. The pulmonary function tests indicate that a patient with chronic bronchitis does not breathe as well as a normal individual, but he breathes better than a patient suffering from emphysema. Many clinicians were already aware of this. Dr. Ronald Gibson is responsible for the chapter on "The Heart in Chronic Bronchitis and Emphysema." The book concludes with Dr. John Horder's contribution on "Aspects of Chronic Bronchitis in General Practice."

Thirty shillings is a large price to pay for this small, although well produced volume.

G. E. BEAUMONT.

Selektive Lungenangiographie in der Praoperativen Diagnostik und in der Inneren Klinik. By Professor Dr. WILHELM BOLT, Professor Dr. WERNER FORSSMANN and Dr. HANS RINK. Stuttgart: Georg Thieme Verlag. 1957. Pp. 199.

This excellent monograph on selective pulmonary arteriography is written by a team of experts, including Professor Forssman (Nobel prize winner), who was the first to pass the cardiac catheter in man and to obtain a pulmonary arteriogram.

The book opens with a detailed description of technique and indications for selective pulmonary arteriography. These general points are followed by an analysis of the various pulmonary vascular patterns and specific pathological appearances of the pulmonary arteries and veins in various pulmonary disorders, acquired and congenital heart disease. The results of this new method of investigation of the lesser circulation are further correlated with lung function studies and hæmodynamic findings of cardiac catheterisation. A wide selection from a total of 2,000 pulmonary arteriograms forms the basis of this analysis.

Pre- and post-operative angiographic studies of patients who were submitted to various forms of thoracic surgery are of particular interest, and so are the findings in the lesser circulation in patients with acquired and congenital heart disease complicated by pulmonary hypertension.

Reproductions throughout the book are of the highest quality, a great tribute to the publishers. For those who are interested in the pathological physiology of the lesser circulation this volume is a most valuable and timely addition to the many publications which have appeared in recent years.

R. E. STEINER.

Current Medical Research. A reprint of the articles of the Report of the Medical Research Council for the year 1955-56. London: H.M. Stationery Office. 2s. 6d. net.

IN the first pages of this publication an account is given of the Council's development of policy in the last few years in regard to clinical research, and of the various ways in which allocations of grants are determined in order to further research, whether centrally organised or decentralised.

The later and major part of the brochure consists of reprints of articles from the Council's Report to Parliament for the year.

The field covered by the thirteen reviews is extensive, including as it does observations on Lung Cancer of special interest to readers of this journal; Poliomyelitis Vaccination; Vaccination againt Pertussis; Protein Deficiency in Man; Growth and Renal Function; Abnormal Hæmoglobins; Microbial Genetics; Radiation and Transplantation Immunity; Radiation and Leukæmia; Chemical Aspects of Antibiotics; and Mass Spectrometry for Gas Analysis in Respiratory Research and Clinical Practice.

A considerable amount of recorded fact has in these reprints been concentrated into relatively small space, and the articles are well documented. It seems hardly likely, in our view, that they will make much appeal to the lay public; but to the genuine medical or scientific research worker, in the earlier stages of his or her career, this publication should prove a valuable mine of information and a real help in constructing the initial plan of investigation.

MAURICE DAVIDSON.

Guide Technique et Topographique d'Exploration Bronchologique (*Bronchoscopie et Bronchographie*). By JEAN IOANNOU, Medecin-adjoint au Sanatorium de Chevilly; Attaché de Bronchoscopie à la Clinique de Pneumo-phtisiologie de la Faculté de Paris. In collaboration with A. DUCHET-SUCHAUX and A. PINELLI. Preface by Docteur P. CHADOURNE. Paris: Masson et Cie. Pp. 114. 66 figs. Fr. 1,400.

This monograph is presented exactly twenty-five years after the publication of the classical work of Sicard and Forestier on the use of Lipiodol in diagnosis and treatment. The interval has seen great advances in our knowledge in many respects, notably in the development of the technique of bronchoscopy, in our understanding of the anatomy of the bronchial system and, not least in importance, in the chemical composition of the contrast media which can be employed in bronchography.

Bronchoscopy and bronchography have now become a basic feature of the investigation of chest disease. They provide information which is fundamental in considering problems of diagnosis, location of lesions and treatment.

About a third of the book is devoted to a detailed consideration of the anatomy of the bronchial tree, with its variations in health and in disease.

Emphasis is laid on the necessity for a full understanding of the topographical anatomy of the bronchi, especially when one is attempting to interpret tomobronchograms, the value of which is repeatedly stressed.

The illustrations are clearly reproduced and easy to follow. The price of the book seems to be a trifle heavy when one considers the somewhat limited scope of the material presented.

JAMES MAXWELL.

Le Traitement de la Tuberculose de l'Enfant. Paris: Masson et Cie. Pp. 354. 80 figs. Fr. 2,500.

This transcription in French of the proceedings of the seminar on the treatment of tuberculosis in childhood, held in Paris in 1955 under the auspices of the Centre International de l'Enfance, is in the reviewer's opinion by far the best book on tuberculosis in childhood yet published, and this despite the language difficulty, much repetition and some inferior contributions on uninteresting topics. Indeed, the use of French is an advantage, leading many of the contributors (who were drawn from many countries) to adhere to the fine tradition of French medical writing, so much more lucid and balanced than our own. This is particularly evident in the introductions to the papers, where each author takes pains to give an accurate résumé of the field of knowledge to which his work is a contribution: thus what is established is stated lucidly, repeatedly and with authority, while the fact that the papers were given to an audience of experts from all over the world makes it easy for the reader to gauge the quality of the new material presented. Of particular interest are the sections on the medical and surgical treatment of primary glandular complexes, both in the neck and thorax, the survey of the world situation, and the reports of various laboratory workers on recent advances in basic scientific knowledge of the subject. This is an essential up-to-date reference book for anyone responsible for the treatment of tuberculous children and for those teaching on the subject. It is surprisingly well produced for the price.

J. A. DAVIS.

Tuberculosis Nursing. By JESSIE G. EYRE. London: H. K. Lewis and Co. Ltd. 1957, 2nd edition. Pp. 354. 25s.

This book is practical, informative and highly readable. It is difficult to keep pace with the contemporary rapid changes in treatment, and because of this some of the chapters are not as up-to-date as they might be. For example, there is no doubt that pneumothorax treatment is on the decline and the maintenance of an artificial pneumothorax with a tension cavity is certainly undesirable. From one's own experience, the statement that " patients taking their premature discharge from hospital would almost certainly break down " is shown to be at present inapplicable. It is now recognised that most patients can have satisfactory domiciliary treatment under supervision, provided they are co-operative and their home conditions permit. The chapters on domiciliary treatment are not as comprehensive as they might be. The book is eminently practical, but perhaps more emphasis might have been made on the co-operation between the family doctor, chest physician, health visitor and occupational therapist.

FRANCIS M. WILLIAMS, S.R.N.

Postural Drainage. By E. WINIFRED THACKER. London: Lloyd-Luke (Medical Books) Ltd. 1956. Pp. 56. Illus. 8s. 6d.

This is an extremely useful and well-presented book. It is fully illustrated with excellent photographs and diagrams. The photographs, although small, show every detail of the postures and of how to get enough comfort for patients to be able to relax. It is good to see this important point stressed and the necessity for relaxation explained. The anatomy and the physiology and the striking diagrams accompanying the postural drainage positions are simple and clear. Instructions about breathing and coughing are brought out succinctly. While all would agree that persistent forced expirations are irritating and therefore contra-indicated, it is not accepted by everyone that " the mouth must be shut " during expirations (in all cases other than those with nasal obstruction). In diaphragmatic breathing it is often found in the early training that allowing the patient to breathe out *softly* through parted lips and teeth helps the natural relaxation which should be the first part of every expiration. Miss Thacker explains and wisely stresses the need for enough time and localised effort for good inspiration into the required area.

In the surgical section, Miss Thacker's wide experience of the treatment of surgical chest patients is apparent. Besides the postures she had described in detail her methods for lowering and raising patients, of holding them for coughing, etc. A short practical chapter is included on an excellent method of drainage for small children and babies—with delightful photographs—and for " aged and grossly emphysematous patients," and the appendix includes post-abdominal surgical postural drainage.

This comprehensive, much-needed little book will surely receive the success it deserves.

J. M. W. REED.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

Chronic Bronchitis, Emphysema and Cor Pulmonale. By C. H. Stuart Harris and T. Hanley. 1957. Pp. 245. 42s. Bristol: John Wright and Sons Ltd.

Die Jungencysten. By J. Zaaeck and H. Riegel. 1958. Pp. 138. DM. 34. Berlin: Waltes de Gunyter and Co.

Chemotherapy and Chemoprophylaxis in Tuberculosis Control. Report of a Study Group. World Health Organization. Technical Report Series, 1957, No. 141. Pp. 12. 1s. 9d. Sw. Fr. 1.00 or $0.30.

Annual Report of City Medical Officer of Health, 1956. Durban: City Health Dept. Pp. 117. Illus.

Tuberculosis Index (*including Chest Diseases*). Qtrly. Dec. 1957. Vol. 12. No. 4. Pp. 689. 25s. yearly. London: NAPT.

Lehrbuch der Rontgenologischen Differential-diagnostik. Band 1. *Erkrankungen der Brustorgane.* By Prof. Dr. Werner Teschendorf. Koln. Pp. 1183, Illus. DM. 210. Stuttgart: Georg Thieme Verlag.

REPORTS

MINISTRY OF HEALTH

A FURTHER reduction in the death rate from tuberculosis and an increase from lung cancer are reported by Sir John Charles, Chief Medical Officer of the Ministry of Health, in his annual report.*

TUBERCULOSIS

Deaths from and notifications of tuberculosis showed a further fall in 1956. Deaths from all forms of tuberculosis numbered 5,375, compared with 6,492 in 1955 and 22,850 ten years ago. Of the deaths in 1956, 4,853 were from respiratory tuberculosis. The number of cases of tuberculosis notified was 35,504, a decline over the previous year of 7 per cent.

CANCER

Recent work on the relationship of cigarette smoking to *lung cancer* confirmed earlier inferences that there is an association betewen the two, though its precise nature has not yet been determined.

In 1956, 92,710 persons died of cancer (48,935 males and 43, 775 females). Of these, 18,186 (15,615 males and 2,571 females) died of cancer of the lung, bronchus etc. The male deaths represented a death rate of 726 per million living and the female deaths 111 per million living. In 1920 the comparable rates were 17 and 10. The increase in male deaths in the year was 5·4 per cent.

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* Report of the Ministry of Health for the year ended December 31, 1956; Part II; On the State of the Public Health. Command 325. H.M.S.O. Price 9s.

THE REGISTRAR-GENERAL'S QUARTERLY RETURN*

THE Registrar-General's Quarterly Return relating to England and Wales for the September quarter, 1957, includes references both to Tuberculosis and Bronchitis.

TUBERCULOSIS

A table included in the Return gives the numbers of deaths from tuberculosis, the new cases notified and the death rates in England and Wales and various other countries in Europe per 100,000 population in the years 1950 to 1955. The table shows that the death rate from tuberculosis has fallen by more than 50 per cent. since 1950 in all the countries for which 1955 figures are shown, except Austria and Switzerland. Only Denmark and the Netherlands had lower rates than England and Wales in 1955.

BRONCHITIS*

Deaths from bronchitis in the *June* quarter, 1957, numbered 4,752 (3,405 males and 1,346 females).

A map is included in the Return showing the death rates from bronchitis of persons aged 65-74 in Greater London and in the regions of England and Wales in 1955. This shows that the highest death rates from bronchitis were experienced by the North-western region and by South-east Wales, followed by the East and West Ridings and the Midland regions and by Greater London. The regions with the lowest death rates were the South-eastern (excluding Greater London, the Southern, the South-western and the Eastern.

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* The Registrar-General's Quarterly Return, No. 435. H.M.S.O. 1s. 6d. net.

WORLD HEALTH ORGANIZATION

CHEMOTHERAPY AND CHEMOPROPHYLAXIS IN TUBERCULOSIS CONTROL: REPORT OF A STUDY GROUP

THIS report gives the conclusions of a group of experts who were asked to evaluate the knowledge at present available on chemotherapy and chemoprophylaxis as public health measures in tuberculosis control.

A programme for the control of tuberculosis must be based on surveys to ascertain the prevalence of the disease among the different population groups. The Study Group therefore lays particular emphasis on this point and stresses the necessity for improving present survey methods.

The organisation of a chemotherapy programme is a complex matter, and for this reason each country should carry out experiments in limited areas before embarking upon a country-wide programme. The Group has therefore drawn up a minimum programme for areas where tuberculosis is very prevalent and hospital services are inadequate. Daily administration of isoniazid (INAH) in association with PAS gives the best results in out-patient or domiciliary treatment. If PAS cannot be used, INAH, the report states, can be administered, alone. The report and the annex thereto contain practical information with regard to the rationale of administration of INAH alone, particularly when it is used as a prophylactic.

The reports ends with an account of the important problems which still await a solution and the lines along which research on these questions should be developed.

World Health Organization: Technical Report Series, 1957, No. 141, 12 pages. Price 1s. 9d., Sw. fr. 1.00 or $0.30.

NOTES AND NOTICES

THIRD INTERNATIONAL CONGRESS OF PHOTOFLUOROGRAPHY

This Congress, organised in co-operation with the International Society of Photofluorography and the International Union against Tuberculosis, will take place in Stockholm from August 20 to 23, 1958, under the Presidency of Prof. Carl Wegelius.

Among the subjects to be dealt with at the Congress are:

The Future Potentialities of Photofluorography.
The use of Photofluorography in:

- (*a*) Diseases of the chest
- (*b*) Cardiology
- (*c*) Early detection of tumours
- (*d*) Preventive and occupational medicine.

The Course will be held at the Royal Institute of Technology, Valhallavagen 79, Stockholm 70, and the Secretaries General of the Congress are Dr. Ingvar Stahle and Dr. Hanns J. Bauer.

JOINT TUBERCULOSIS COUNCIL

The report of the Public Health Committee on " Collection and Sterilisation of Tuberculous Sputum in Hospital and at Home " has now been published and can be obtained from the Secretary of the Council. It is emphasised that despite all progress in treatment the control of infection must be linked with the proper disposal of sputum, and instructions for the collection, sterilisation and disposal of sputum are well tabulated in this document.

NAPT COMMONWEALTH CHEST CONFERENCE

As previously noted, H.R.H. the Duchess of Kent, the President, is to open the Conference at the Royal Festival Hall on July 1 in connection with the World Anti-Tuberculosis Campaign. The subject is being discussed by:

Sir Kenneth Cowan (Scotland)
Sir Harry Wunderly (Australia)
Dr. B. A. Dormer (S. Africa)
Dr. Johannes Holm (World Health Organisation)
Dr. J. H. F. Jayasuriya (Ceylon) and
Professor R. Neubauer (Yugoslavia)

An extensive exhibition during the Conference, with practical illustrations of all forms of chest disease, is being arranged.